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Hijacking Cell Death: A Viral Ferroptosis Modulation Index

Bahman Aghcheli*

Infectious Diseases Research Center, Gonabad University of Medical Sciences, Gonabad, Iran

***Corresponding author:** Bahman Aghcheli, Infectious Diseases Research Center, Gonabad University of Medical Sciences, Gonabad, Iran

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ABSTRACT

Despite growing evidence that ferroptosis is an iron-dependent form of regulated cell death, its role in viral pathogenesis has not been comprehensively characterized. Existing reviews have detailed ferroptosis mechanisms such as system Xc-/GPX4, p53, FSP1, and iron/lipid pathways, as well as inducers, inhibitors, and their involvement in tumors, neurodegeneration, acute kidney injury, and specific infections. However, these reviews largely lack classification or predictive linkage across viral families. A unifying framework that integrates these observations across diverse viral families and links ferroptotic modulation to viral replication strategies and clinical phenotypes is still absent. To address this, we integrated evidence from fourteen viral families and developed the Ferroptosis Modulation Index, a literature-based conceptual framework that classifies the net viral impact on ferroptosis along a continuum from pro-ferroptotic (+1 to +5) to anti-ferroptotic (−1 to −5) according to key molecular domains. High positive FMI scores (e.g., SARS-CoV-2: +4; MPXV: +4) are primarily associated with lytic replication cycles, acute cytopathic effects, and tissue damage, whereas high negative scores (e.g., KSHV: −5; HBV: −4) correspond to viral latency, persistence, and oncogenic potential. The FMI positions ferroptosis as a central axis in host–virus interactions and offers a foundation for hypothesis generation and mechanism-guided intervention strategies. This review synthesizes current evidence, discusses controversies regarding cell death pathway dominance, identifies critical research gaps, and outlines future directions for translating the FMI from a conceptual model to a tool.

Keywords: Ferroptosis; Virus Diseases; Therapeutics; Host Microbial Interactions; PANoptosis

Abbreviations: RCD: Regulated Cell Death; GSH: Glutathione; GSSG: Glutathione Disulphide; GPX4: Glutathione Peroxidase 4; Nrf2: Nuclear Factor Erythroid 2-Related Factor 2; SLC7A11 (Solute Carrier Family 7 Member 11 (System Xc^- subunit)), TfR1 (Transferrin Receptor 1); NCOA4 (Nuclear Receptor Coactivator 4), ACSL4 (Acyl-CoA Synthetase Long-Chain Family Member 4), LOXs (Lipoxygenases); PUFA (Polyunsaturated Fatty Acid); FSP1 (Ferroptosis Suppressor Protein 1); CoQ10 (Coenzyme Q10); ROS (Reactive Oxygen Species); L-ROS (Lipid Reactive Oxygen Species); Keap1: Kelch-like ECH-associated Protein 1; PTGS2: Prostaglandin-Endoperoxide Synthase 2

Tweetable Abstract

Introducing the Ferroptosis Modulation Index (FMI), a new framework classifying how viruses manipulate cell death. Pro-ferroptotic viruses (like SARS-CoV-2) cause tissue damage; anti-ferroptotic ones (like KSHV) promote cancer. FMI guides therapy: inhibit ferroptosis for acute disease, induce it for latent infection & cancer. #ferroptosis #virology #FMI (Graphical Abstract).

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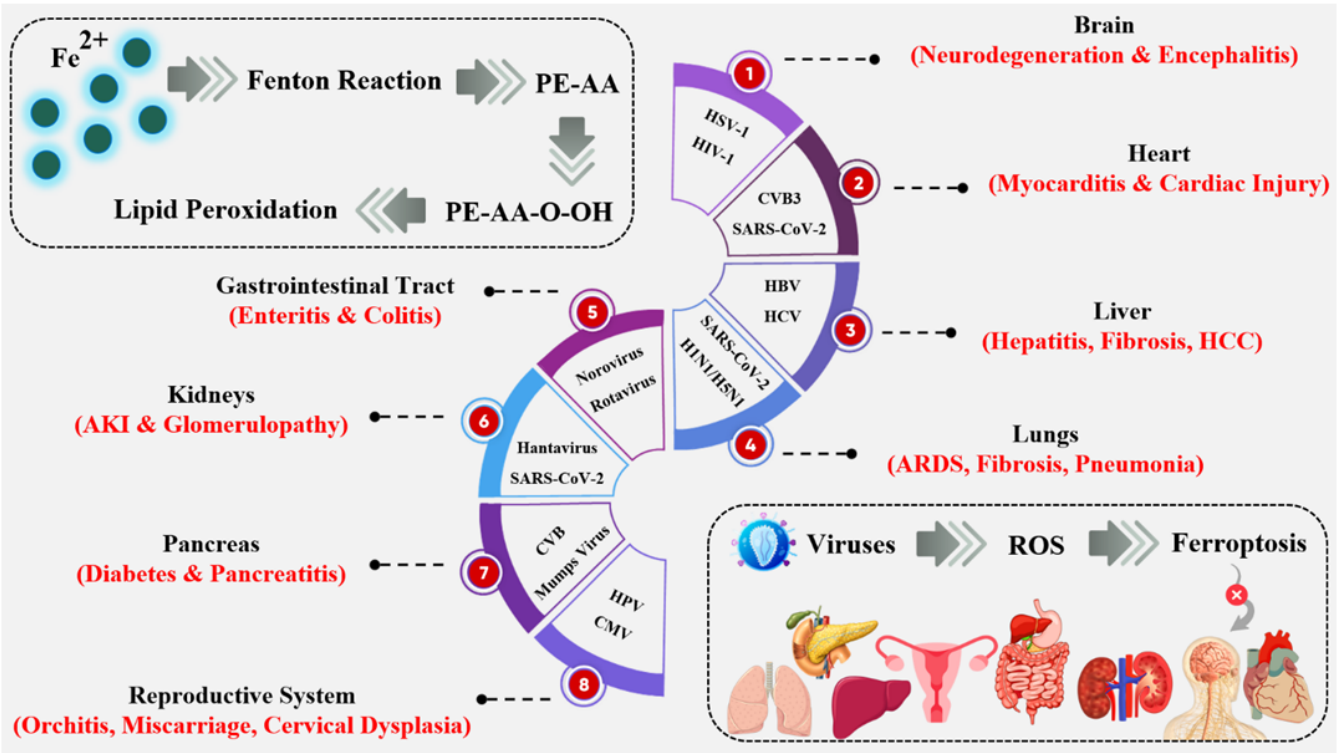

Graphical Abstract.

Contribution to the Field Statement: Viruses and Ferroptosis: How Viruses Control Cell Death and what it Means for Treatment

While viral modulation of programmed cell death is well-documented, a coherent model connecting these strategies to specific disease phenotypes remains elusive. Existing literature catalogs how individual viruses influence ferroptosis, an iron-dependent form of cell death, yet fails to synthesize these findings into a predictive or therapeutically actionable framework. To bridge this gap, we propose the Ferroptosis Modulation Index (FMI), a novel scoring system that quantifies the propensity of a virus to enhance or suppress ferroptotic pathways. Our analysis reveals a consistent trend: viruses associated with acute, immunopathic disease (e.g., SARS-CoV-2) demonstrate pro-ferroptotic tendencies, whereas those establishing chronic infection and oncogenesis (e.g., Kaposi's sarcoma-associated herpesvirus) predominantly exhibit anti-ferroptotic activity. By translating discrete molecular observations into a unified strategic map, the FMI directly links viral pathogenesis mechanisms to clinical outcome. This framework offers a rationale for targeted therapeutic intervention using ferroptosis inhibitors in acute viral damage or inducers against latent reservoirs and establishes a common paradigm to advance precision antiviral strategies.

Introduction

Ferroptosis has emerged as a critical and distinct form of regulated cell death that viruses have evolved to manipulate, representing a new frontier in understanding host-pathogen interactions [1]. Metal-dependent cell death pathways encompass a group of regulated cell death (RCD) pathways, including ferroptosis (iron), cuproptosis (copper), zincosis (zinc), manganism (manganese), and calcicoptosis (calcium), highlighting the critical importance of metal homeostasis in cell survival [2]. Viral infections often activate a spectrum of regulated cell death (RCD) pathways [3]. The innate immune system triggers programmed cell death mechanisms in response to microbial invasions, and viruses frequently manipulate cellular metabolism, potentially triggering diverse cell death pathways, such as PANoptosis, a coordinated combination of pyroptosis, ferroptosis, apoptosis, and necroptosis [4]. This integrated cell death response represents a molecular tug-of-war between host defense and viral survival strategies. Distinct from apoptotic cell death, ferroptosis is characterized morphologically by mitochondrial shrinkage with intact outer membranes and is regulated biochemically by key factors such as p53, nuclear factor erythroid 2-related factor 2 (Nrf2), and ferritinophagy [5,6]. The core biochemical signature of ferroptosis involves the lethal accumulation of lipid peroxides driven by iron-dependent Fenton chemistry, depletion of glutathione (GSH), and inactivation of the key antioxidant enzyme glutathione peroxidase 4 (GPX4) [7-9].

This process can be induced by compounds that inhibit system Xc- (e.g., erastin), directly target GPX4 (e.g., RSL3), or deplete endogenous antioxidants like coenzyme Q10 (CoQ10) [9,10]. Conversely, ferroptosis is inhibited by iron chelators (e.g., deferoxamine) and radical-trapping antioxidants like ferrostatin-1 and liproxstatin-1 [11,12]. Recent comprehensive reviews have summarized ferroptosis hallmarks, regulatory pathways (e.g., GSH/GPX4 inhibition, iron via TFRC/DMT1/FPN/ferritinophagy, lipid via ACSL4/LPCAT3/LOX, FSP1-CoQ10, p53/SLC7A11, autophagy/NCOA4), inducers (erastin/RSL3/FIN56/FINO2), inhibitors (Fer-1/liproxstatin-1/DFO/vitamin E), and associations with tumors, neurological diseases, Acute Kidney Injury (AKI), Ischemia/Reperfusion (I/R), and inflammation, however, no unifying quantitative model exists to classify viral modulation strategies, link them to replication phenotypes (lytic dissemination vs. latency/oncogenesis), or guide context-specific therapy [13-19]. The FMI is not merely descriptive; it provides a direct, mechanistic rationale for therapeutic intervention. The framework logically guides a bifurcated strategy: adjuvant ferroptosis inhibition for acute diseases driven by pro-ferroptotic viruses versus therapeutic ferroptosis induction for chronic infections and malignancies associated with anti-ferroptotic viruses.

A central and unresolved question in virology is why different viruses exert opposing effects on this pathway. We propose and investigate a unifying "ferroptosis trade-off" hypothesis, which posits that the direction of ferroptosis modulation is an evolutionary adaptation aligned with viral replication strategy: lytic, rapidly disseminating viruses promote ferroptosis to facilitate cell lysis and release of progeny, whereas latent or oncogenic viruses suppress ferroptosis to ensure long-term cellular survival and persistence. This review systematically investigates the evidence and introduces the FMI as a novel, literature-derived tool to objectively classify and compare viral effects. We further extend the FMI from a descriptive framework to a predictive and actionable model by delineating its direct therapeutic implications for both acute and chronic viral diseases. However, the field currently lacks consensus on whether ferroptosis is a primary driver of pathology or a secondary consequence of broader metabolic disruption, and whether its modulation is a core viral strategy or an epiphenomenon in specific contexts. This review aims to present a complete overview of the state of the art, discussing these fundamental questions, different perspectives and controversies, current research gaps, and potential future developments in this emerging field.

Development and Calculation of the Ferroptosis Modulation Index

The Ferroptosis Modulation Index (FMI) was developed de novo as a quantitative and reproducible tool to classify viral interactions with ferroptosis objectively. The scoring system is based on three fundamental molecular domains of ferroptosis regulation:

1. Iron Homeostasis Dysregulation (e.g., changes in transferrin receptor 1 (TfR1) expression, nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy, labile iron pool levels);
2. Lipid Peroxidation Modulation (e.g., alterations in acyl-CoA synthetase long-chain family member 4 (ACSL4) or lipoxygenase (LOX) activity, accumulation of lipid peroxidation products like malondialdehyde (MDA) or 4-hydroxynonenal (4-HNE)); and
3. Antioxidant System Manipulation (e.g., effects on glutathione peroxidase 4 (GPX4) activity, solute carrier family 7 member 11 (SLC7A11) expression, glutathione (GSH) levels, or Nrf2 pathway activation).

Each virus was assigned a score for each domain based on the strength and consistency of the aggregated experimental evidence. The scoring scale for each domain ranged from -5 to +5: a score of +5 or -5 indicated strong, consistent, and directly demonstrated pro- or anti-ferroptotic activity across multiple studies, often with in vivo validation; a score of +3 or -3 indicated clear and consistent evidence from in vitro or in vivo studies; a score of +1 or -1 indicated weak, indirect, or preliminary evidence; a score of 0 indicated no significant effect or a lack of data.

The overall FMI for a virus was calculated as the arithmetic mean of its three domain scores:

$$\text{FMI} = \frac{(Iron\ Score + Lipid\ Score + Antioxidant\ Score)}{3}$$

For viruses demonstrating well-documented, context-dependent modulation (e.g., different effects in different cell types or tissues), separate FMI scores were calculated for each context. The complete scoring rationale and domain-level evidence for each virus are documented in a supplementary table to ensure full transparency and reproducibility. In contrast to qualitative discussions of virus-specific iron/antioxidant effects, the FMI aggregates evidence strength across studies (strong in vivo = ±5; preliminary = ±1; none = 0) into a net arithmetic mean score per virus/context. Limitations include evolving evidence and subjectivity; future meta-analyses could refine it.

Molecular Foundations of Ferroptosis

Ferroptosis is a distinct, iron-dependent form of regulated cell death driven by the lethal accumulation of lipid peroxides, particularly through the peroxidation of polyunsaturated fatty acids (PUFAs) in cellular membranes [20]. Unlike apoptosis, necrosis, or autophagy, ferroptosis lacks hallmark features such as chromatin condensation, cell swelling, or autophagosome formation [21]. Its core biochemical pathways reflect a toxic interplay between iron metabolism, lipid biochemistry, and antioxidant defense mechanisms [22]. The core biochemical pathways involve a toxic interplay between iron metabolism, lipid biochemistry, and antioxidant defense [23,24].

Iron Metabolism: Intracellular iron overload is a hallmark of ferroptosis. Iron is taken up via transferrin receptor 1 (TfR1) and transported into the cytosol, where it contributes to the labile iron pool (LIP). This redox-active iron catalyzes the Fenton reaction, generating hydroxyl radicals that initiate and propagate lipid peroxidation [21].

Furthermore, ferritinophagy, the autophagic degradation of ferritin mediated by nuclear receptor coactivator 4 (NCOA4), releases stored iron, amplifying the LIP and driving ferroptosis [25].

Lipid Peroxidation: Membrane PUFAs, such as arachidonic acid and adrenic acid, are esterified into phospholipids by enzymes like acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) [26]. These PUFA-containing phospholipids are prime substrates for peroxidation by lipoxygenases (LOXs) or via iron-catalyzed autoxidation, yielding toxic lipid hydroperoxides (L-OOH) that disrupt membrane integrity and function [27].

Antioxidant Defense: The glutathione (GSH)-GPX4 axis is the primary defense against ferroptosis. System Xc-, a cystine/glutamate antiporter composed of SLC7A11 and SLC3A2, imports cystine for GSH synthesis. GPX4 utilizes GSH to reduce lipid hydroperoxides to nontoxic alcohols, thereby preventing lethal peroxidation. Inhibition of system Xc- (e.g., by erastin) or direct inhibition/degradation of GPX4 (e.g., by RSL3 or FIN56) collapses this defense, leading to ferroptosis execution [28]. Parallel antioxidant systems have been identified, including the ferroptosis suppressor protein 1 (FSP1, formerly AIFM2), which regenerates reduced coenzyme Q10 (CoQ10) using NAD(P)H, independently suppressing lipid peroxidation at the plasma membrane [29].

Regulatory Networks: Multiple signaling pathways converge on ferroptosis regulation [30]. The tumor suppressor p53 can promote ferroptosis by transcriptionally repressing SLC7A11, inhibiting cystine uptake, or via the p53-SAT1-ALOX15 axis [31,32]. Conversely, the p62-Keap1-Nrf2 pathway is a major anti-ferroptotic hub, upregulating a battery of antioxidant and cytoprotective genes, including SLC7A11, GPX4, and ferritin subunits [33,34]. The mevalonate pathway supplies isopentenyl pyrophosphate for the maturation of selenocysteine tRNA, which is essential for GPX4 synthesis, linking cholesterol biosynthesis to ferroptosis sensitivity [35]. Viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and human immunodeficiency virus-1 (HIV-1) have been shown to actively disrupt these pathways, thereby sensitizing cells to ferroptotic death and linking this process directly to viral pathogenesis and disease manifestations [36,37]. Figure 1 illustrates the core pathways of ferroptosis, including iron dysregulation (via transferrin receptor 1 (TfR1)/nuclear receptor coactivator 4 (NCOA4)), lipid peroxidation (mediated by ACSL4/lipoxygenases (LOXs)), and antioxidant defense collapse (System Xc^-/GPX4 axis), alongside viral proteins that manipulate these mechanisms to promote or inhibit ferroptosis.

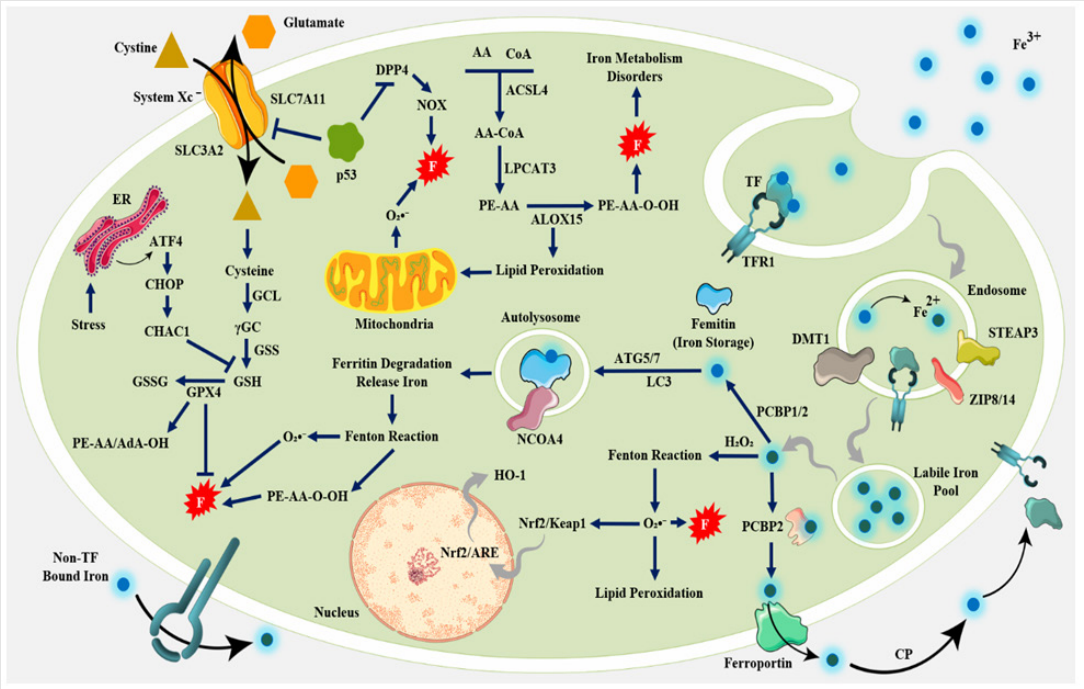

Figure 1: Molecular mechanisms of ferroptosis and viral modulation. The figure depicts key ferroptosis pathways:

(1) Iron homeostasis dysregulation (e.g., TfR1-mediated uptake, NCOA4-driven ferritinophagy, and Fenton reactions);

(2) Lipid peroxidation via ACSL4/LPCAT3-mediated PUFA incorporation and LOX/ROS-induced membrane damage;

(3) Antioxidant system failure (System Xc GSH-GPX4 axis disruption, FSP1-CoQ10 backup pathway). Viral proteins (e.g., SARS-CoV-2 ORF3a, HBV miR-222) hijacking these pathways, either inducing ferroptosis by depleting GSH/GPX4 or suppressing it via Nrf2 activation. Mitochondrial shrinkage and ROS accumulation are hallmarks of ferroptotic cell death.

FMI-Based Classification of Viral Strategies

This integrative scoring framework highlights recurring patterns in the literature that are not readily apparent from earlier exploratory overviews, including the tendency of lytic viruses to adopt pro-ferroptotic strategies (for example, SARS-CoV-2, FMI +4, through ORF3a-mediated disruption of antioxidant defenses and induction of ferritinophagy), in contrast to the anti-ferroptotic mechanisms commonly employed by persistent or oncogenic viruses (such as KSHV, FMI −5, via vIL-6–associated upregulation of SLC7A11). Viewed in this context, the Ferroptosis Modulation Index (FMI) serves as a unifying, literature-derived framework for organizing existing evidence and for classifying viruses into distinct strategic categories, as summarized in Table 1.

Table 1: Viral Modulation of Ferroptosis with Ferroptosis Modulation Index (FMI) Scoring.

Category	Virus	FMI	Key Mechanisms	Molecular Targets/ Pathways	Clinical/Pathological Outcome	Ref
Pro-Ferroptotic	SARS-CoV-2	+4	ORF3a disrupts Keap1-Nrf2; N inhibits SLC7A11; induces ferritinophagy	↑ Fe^{2+}, ↑ lipid ROS, ↓ GPX4, ↓ GSH	ARDS, multi-organ damage, viral dissemination	[37,38]
	HIV-1	+4	Tat upregulates ACSL4 & TfR1; depletes GSH in microglia	↑ ACSL4, ↑ TfR1, ↓ GSH, ↑ lipid peroxidation	Neuroinflammation, immune evasion, neurocognitive decline	[36,40]
	MPXV	+4	Iron overload, GSH depletion, PTGS2 upregulation	↑ Fe^{2+}, ↑ MDA, ↑ PTGS2, ↓ GSH/GSSG	Enhanced replication, inflammatory pathology, vesicular rash	[39]
	Influenza A	+3	Disrupts Xc−/GPX4; upregulates TfR1 via HA	↑ TfR1, ↑ ACSL4, ↓ GPX4 activity	Pneumonia, acute lung injury, ferroptosis-dependent lysis	[71]
	Enteroviruses	+2	Upregulates ACSL4 via Sp1-mediated TfR1 expression	↑ TfR1, ↑ ACSL4, ↑ lipid ROS	Myocarditis, enhanced viral replication	[72,73]
	NDV	+4	Activates p53-SLC7A11-GPX4 axis; induces ferritinophagy	↑ NCOA4, ↑ Fe^{2+}, ↓ SLC7A11/GPX4	Oncolytic tumor cell death	[74]
	ZIKV	+3	BLVRB converts Fe^{3+}→Fe^{2+}; ER lipid peroxidation via NS4A/NS4B	↑ NS4A/NS4B, ↑ LPO, ↑ Fe^{2+}	Microcephaly, neuronal damage, viral spread	[75]
	ISKNV	+3	Downregulates GPX4; upregulates ACSL4	↓ GPX4, ↑ ACSL4	Enhanced replication in aquaculture	[76]
	PRRSV	+2	Promotes ferroptosis via DDX3X-mediated mitochondrial damage	↑ TFRC, ↓ GPX4, ↑ mitochondrial ROS	Enhanced viral propagation, respiratory disease	[75]
Anti-Ferroptotic	KSHV	-5	vIL-6 stabilizes SIRT3-SERBP1; upregulates SLC7A11	↑ SLC7A11, ↓ ACSL4, ↓ lipid ROS	Kaposi sarcoma, lymphoma persistence, tumor survival	[41]
	HBV	-4	HBx silences SLC7A11 via EZH2/H3K27me3; miR-222 silences TfR1	↓ SLC7A11, ↓ TfR1, ↓ lipid ROS	Chronic hepatitis, liver fibrosis, hepatocellular carcinoma	[42]
	EBV	-4	Activates Nrf2/GPX4 via p62-Keap1 & LMP1 signaling	↑ Nrf2, ↑ GPX4, ↑ SLC7A11	Nasopharyngeal carcinoma, lymphoma persistence	[43]
	HCMV	-3	pUL138-USP24 inhibits NCOA4, blocking ferritinophagy	↓ NCOA4, ↓ LIP, ↓ ferritinophagy	Persistent infection, congenital defects	[44]
	HCV	-3	NS5A upregulates GPX4; downregulates TfR1/DMT1	↑ GPX4, ↓ TfR1/DMT1, ↓ ROS	Chronic infection, liver steatosis, cirrhosis	[77]
	LCMV	-2	Suppresses mTORC2→GPX4 via AKT-GSK3β axis	↓ GPX4, ↓ mTORC2 signaling	Impaired T-cell memory, immune evasion	[78]
	ASFV	-3	Blocks ferroptosis; ferrostatin-1 restores replication	↓ Fe^{2+}, ↓ LPO, suppressed ferroptosis	Sustained infection, hemorrhagic fever	[79]
	RABV/EMCV	-4	Induces lipid droplets via DGAT to sequester AA	↓ cytosolic AA, ↓ lipid peroxidation, ↑ LD formation	Neuronal persistence, neuroinvasion, evasion of ferroptosis	[57]
Context-Dependent	HSV-1 (Lung)	+3	FcRn suppression, iron overload, PTGS2 activation	↑ ROS, ↓ GPX4, ↑ PTGS2	Pneumonitis, acute lung injury, dissemination	[45]
	HSV-1 (Neuron)	-3	Anti-ferroptotic mechanisms; lipid metabolism modulation	↓ lipid peroxidation, ↑ cell survival factors	Neuronal latency, reactivation, encephalitis risk	[80]

Note: ↑: Up regulation, ↓: Down regulation, $NADP^+$: Nicotinamide adenine dinucleotide phosphate, LIP: Labile iron pool, ZIKV: Zika virus, NDV: Newcastle disease virus, IL-6/TNF-α: Interleukin-6/Tumor necrosis factor-alpha.

Ferroptotic Viruses (FMI: +1 to +5): Viruses within this category consistently scored positively, indicating a strategy of ferroptosis induction. SARS-CoV-2 received an FMI of +4, based on strong evidence that its ORF3a protein disrupts the Keap1-Nrf2 antioxidant pathway, its nucleocapsid (N) protein inhibits the SLC7A11 transporter, and it induces ferritinophagy, collectively driving iron overload and lipid peroxidation [37,38]. Similarly, the Monkeypox virus (MPXV) scored +4, with studies demonstrating it induces iron overload, depletes glutathione, and upregulates prostaglandin-endoperoxide synthase 2 (PTGS2); importantly, pharmacological inhibition of ferroptosis was shown to reduce MPXV replication, confirming the functional role of this cell death pathway in its life cycle [39]. HIV-1 also scored +4, with its Tat protein upregulating both ACSL4 and TfR1 while depleting GSH in microglia, contributing to neuroinflammation [36,40]. Other notable pro-ferroptotic viruses include Influenza A virus (FMI: +3), Newcastle disease virus (NDV, FMI: +4), and Zika virus (ZIKV, FMI: +3), all of which manipulate distinct entry points into the ferroptosis pathway to promote cell death and viral spread.

Anti-Ferroptotic Viruses (FMI: -1 to -5): This category encompasses viruses that actively suppress ferroptosis to maintain cellular viability, a strategy common among latent and oncogenic viruses. Kaposi's sarcoma-associated herpesvirus (KSHV) received the lowest score of -5, reflecting its potent, multi-faceted suppression of ferroptosis through mechanisms such as viral interleukin-6 (vIL-6)-mediated stabilization of the SIRT3-SERPINE1 mRNA binding protein 1 (SERBP1) axis and upregulation of SLC7A11 [41]. Hepatitis B virus (HBV) scored -4, utilizing mechanisms like HBx-mediated epigenetic silencing of SLC7A11 and exosomal microRNA-222 (miR-222) silencing of TfR1 to create a ferroptosis-resistant state conducive to chronic infection and carcinogenesis [42]. Epstein-Barr virus (EBV, FMI: -4) and human cytomegalovirus (HCMV, FMI: -3) also employ distinct strategies, such as activating the Nrf2/GPX4 axis or blocking ferritinophagy, respectively, to inhibit ferroptotic death [43,44].

Context-Dependent Viruses

The FMI framework successfully captured viruses whose modulation of ferroptosis is not absolute but varies with cellular context. Herpes simplex virus-1 (HSV-1) is a prime example, exhibiting a pro-ferroptotic phenotype in lung tissue (FMI: +3), which may facilitate dissemination, while displaying an anti-ferroptotic phenotype in neuronal cells (FMI: -3), which likely supports the establishment of lifelong latency [45]. This adaptability underscores the nuanced battlefield of cell death during infection. For instance, while HSV-1 may suppress ferroptosis in neurons to maintain latency, it can simultaneously engage other death pathways; HSV-1 proteins like ICP0 and ICP27 inhibit interferon responses and apoptosis, but the host can counter through sensors like ZBP1, potentially activating PANoptosis as a defense [46]. This nuanced classification underscores the adaptability of viral strategies and highlights the necessity for tissue-specific therapeutic approaches.

FMI as a Predictive Clinical Tool

A key finding of this review is the correlation between a virus's FMI score and its associated disease phenotype. Viruses with high positive FMI scores (≥ +3) were overwhelmingly associated with diseases characterized by acute cytopathic effect and tissue damage, such as the acute respiratory distress syndrome (ARDS) in COVID-19, influenza pneumonia, and viral encephalitis [47-49]. Conversely, viruses with high negative FMI scores (≤ -3) were consistently linked to chronic infections, viral persistence, and malignancy [50-55]. This correlation positions the FMI not merely as a descriptive tool but as a predictive framework with potential prognostic value. It is important to consider that in acute, damaging infections driven by pro-ferroptotic viruses, excessive cell death may not be limited to ferroptosis. Viruses like SARS-CoV-2 and IAV are potent inducers of PANoptosis, a coordinated lytic cell death that can amplify immunopathology through cytokine release [56]. Thus, a high positive FMI may often coincide with a propensity to trigger broader inflammatory cell death programs.

Divergent Perspectives and Current Controversies

A critical discussion point in the field is whether the observed modulation of ferroptosis represents a viral strategy or a host response. One perspective posits that pro-ferroptotic effects are an active viral tactic to facilitate egress and dissemination, as supported by studies showing that inhibiting ferroptosis reduces viral yield (e.g., MPXV). An alternative view suggests that for some acute viruses, ferroptosis may be primarily a detrimental host-driven immunopathological response, which the virus may inadvertently exacerbate or simply tolerate. For anti-ferroptotic viruses, a key controversy lies in determining if ferroptosis suppression is essential for establishing latency or if it is one of several redundant survival pathways co-opted by the virus. Furthermore, the FMI framework inevitably simplifies complex biology; a major controversy centers on the crosstalk and relative contribution of ferroptosis compared to other regulated cell death pathways like apoptosis, pyroptosis, and the integrated PANoptosis. It remains debated whether ferroptosis is the dominant death modality in specific viral infections or a contributor within a broader cell death network.

Novel Mechanisms: Lipid Droplet Hijacking

This indirect anti-ferroptotic strategy, mediated through DGAT-dependent arachidonic acid (AA) sequestration, exemplifies viral mechanisms that extend beyond the canonical iron and glutathione pathways. Several neuroinvasive viruses, including Rabies virus (RABV) and encephalomyocarditis virus (EMCV), exploit this approach by inducing the formation of host lipid droplets through hijacking of di-

acylglycerol acyltransferase (DGAT) [57]. These virus-induced lipid droplets function as sinks for free AA, a polyunsaturated fatty acid highly susceptible to lipid peroxidation, thereby shielding infected cells from ferroptotic death (FMI: -4). The therapeutic relevance of this mechanism is highlighted by studies demonstrating that pharmacological inhibition of DGAT prevents lipid droplet formation, resulting in AA accumulation, activation of ferroptosis, and robust suppression of viral replication [58,59].

Therapeutic Implications of the FMI

The FMI provides a direct, mechanistic rationale for therapeutic intervention, moving beyond description to actionable strategy. By quantifying a virus's net effect on ferroptosis, the FMI logically guides the selection of pharmacological modulators to protect the host or eliminate infected cells, leading to a clear bifurcated therapeutic approach (Table 2).

Table 2: FMI Therapeutic Decision Matrix.

FMI Category	Score Range	Exemplar Viruses	Associated Disease Phenotype	Therapeutic Goal	Candidate Agents / Strategies	Expected Outcome
Pro-Ferroptotic	+4 to +5	SARS-CoV-2, MPXV, HIV-1 (CNS), NDV	Acute cytopathic effect; Severe tissue damage (ARDS, pneumonia, neuroinflammation)	Inhibit Ferroptosis to limit immunopathology	Ferroptosis Inhibitors: Ferrostatin-1, Liproxstatin-1, Deferoxamine, Vitamin E	Reduced tissue injury, improved organ function
	+2 to +3	Influenza A, ZIKV, Enteroviruses	Acute inflammatory disease with a lytic component	Consider Inhibition in severe cases	As above, or antioxidant support (NAC, GSH precursors)	Attenuation of disease severity
Context-Dependent	Variable (e.g., +3 / -3)	HSV-1 (Lung vs. Neuron)	Tissue-specific pathogenesis (pneumonitis vs. latency)	Precision Modulation based on the site of active disease	Lung: Inhibitors; Neuron: Inducers (if targeting reactivation)	Prevention of acute damage; targeting of reservoirs
Anti-Ferroptotic	-2 to -3	HCMV, HCV, LCMV	Chronic persistent infection	Induce Ferroptosis to eradicate persistent cells	System Xc^- Inhibitors: Erastin, Sorafenib, Sulfasalazine	Clearance of persistently infected cells
	-4 to -5	KSHV, HBV, EBV	Viral latency, oncogenesis, fibrosis	Induce Ferroptosis as an anti-cancer/anti-persistence strategy	As above, plus combination therapy with antivirals, chemo, or immunotherapy	Selective killing of transformed cells, tumor suppression
Novel Indirect Anti-Ferroptotic	-4	RABV, EMCV	Neuroinvasion, persistence	Block Viral Hijacking to restore ferroptosis sensitivity	DGAT Inhibitors (e.g., Pradigastat); AA metabolism modulators	Inhibition of viral replication, sensitization to immune clearance

Note: ARDS: Acute Respiratory Distress Syndrome; CNS: Central Nervous System; NAC: N-Acetylcysteine; GSH: Glutathione; DGAT: Diacylglycerol Acyltransferase; AA: Arachidonic Acid

For Pro-Ferroptotic Viral Infections (FMI ≥ +2): In acute infections driven by lytic, pro-ferroptotic viruses such as SARS-CoV-2, Influenza A, and MPXV, excessive ferroptosis is a major contributor to immunopathology and tissue damage (e.g., in ARDS, pneumonia, encephalitis). In these contexts, adjuvant therapy with ferroptosis inhibitors (e.g., ferrostatin-1, liproxstatin-1, deferoxamine) holds significant promise. The goal is to dampen the cytopathic effect and inflammatory cascade driven by ferroptotic cell death, thereby preserving tissue integrity and improving clinical outcomes. However, given the interconnected nature of cell death pathways, therapeutic inhibition may need to be broad. For example, in severe COVID-19 or influenza, where PANoptosis contributes to cytokine storms, combining ferroptosis inhibitors with agents that target other components of the PANoptosome (e.g., caspase or RIPK inhibitors) could provide superior protection against immunopathology [60].

For Anti-Ferroptotic Viral Infections (FMI ≤ -2): In chronic infections and virus-associated malignancies driven by viruses like KSHV, HBV, EBV, and HCV, the suppression of ferroptosis is a key mechanism enabling cellular persistence and oncogenic transformation. Here, the therapeutic goal shifts to therapeutic induction of ferroptosis. Pharmacological agents that inhibit system Xc^- (e.g., erastin, sulfasalazine), deplete GPX4 (e.g., RSL3), or disrupt viral anti-ferroptotic mechanisms can selectively sensitize and eliminate these "ferroptosis-addicted" infected or transformed cells. This strategy is compelling for combination therapy, pairing ferroptosis inducers with standard antivirals, chemotherapy, or immunotherapy. Inducing

ferroptosis in these contexts could synergize with strategies aimed at triggering other death pathways. For instance, in virus-associated cancers, simultaneously activating ferroptosis and PANoptosis (e.g., via TNF-α/IFN-γ inducers) could overcome the profound resistance to single-pathway cell death that characterizes many tumors [61].

Context-Dependent and Emerging Strategies: For viruses like HSV-1, therapeutic modulation must be tissue-targeted. Furthermore, the discovery of indirect anti-ferroptotic mechanisms, such as lipid droplet hijacking, reveals novel drug targets (e.g., DGAT inhibitors) [62,63]. Future FMI-guided therapy will therefore depend on accurate diagnostic stratification using biomarkers of ferroptosis to apply the correct modulator in the correct clinical context.

The therapeutic implications of this framework are direct and actionable. For infections driven by pro-ferroptotic viruses (high positive FMI), adjuvant therapy with ferroptosis inhibitors (e.g., ferrostatin-1, liproxstatin-1) holds promise for mitigating immunopathology and tissue damage. Conversely, for diseases associated with anti-ferroptotic, persistent viruses (high negative FMI), and therapeutic induction of ferroptosis (using agents like erastin, RSL3, or sorafenib) represents a promising strategy to selectively eliminate infected or transformed cells, particularly in virus-associated cancers. The context-dependent nature of modulation for some viruses further underscores the future need for personalized, biomarker-guided therapeutic approaches.

Conclusion

This comprehensive review investigated the current evidence to present a novel and quantitative framework, the Ferroptosis Modulation Index (FMI), for understanding viral manipulation of cell death. The analysis confirms the "ferroptosis trade-off" hypothesis, demonstrating that a virus's replication strategy powerfully predicts its interaction with this pathway. The FMI successfully classifies viruses into clinically relevant categories, with high positive scores predicting acute, lytic diseases and high negative scores predicting chronic, persistent, and oncogenic outcomes. This framework bridges a critical gap between molecular mechanism and clinical phenotype in viral pathogenesis. Importantly, this review situates ferroptosis within the broader spectrum of regulated cell death, particularly highlighting its potential intersection with the integrated pathway of PANoptosis. This perspective is crucial, as the ultimate pathological outcome of an infection likely depends on the net balance and crosstalk between multiple cell death modalities that viruses must either exploit or evade. The therapeutic implications of this framework are direct and actionable. For infections driven by pro-ferroptotic viruses (high positive FMI), adjuvant therapy with ferroptosis inhibitors (e.g., ferrostatin-1, liproxstatin-1) holds promise for mitigating immunopathology and tissue damage.

Conversely, for diseases associated with anti-ferroptotic, persistent viruses (high negative FMI), and therapeutic induction of ferroptosis (using agents like erastin, RSL3, or sorafenib) represents a promising strategy to selectively eliminate infected or transformed cells, particularly in virus-associated cancers. The context-dependent nature of modulation for some viruses further underscores the future need for personalized, biomarker-guided therapeutic approaches. By framing viral interactions within the FMI, this review clarifies fundamental concepts, highlights areas of divergent interpretation, and underscores the direct link between molecular mechanism and clinical phenotype. The proposed therapeutic strategy, inhibiting ferroptosis in acute disease and inducing it in chronic infection, emerges as a logical development from this study.

Future Directions

To adapt the FMI framework from a conceptual model to a clinical tool, several future research directions are paramount. Prospective clinical studies are needed to validate the correlation between viral FMI scores and patient outcomes across a range of infections. Research must focus on developing safe and effective FMI-guided combination therapies, such as pairing ferroptosis inducers with existing antivirals or immunotherapies for cancers associated with EBV or KSHV. Integrating the FMI with multi-omics data (e.g., lipidomics, transcriptomics of patient samples) and machine learning could enable precise patient stratification and the identification of novel predictive biomarkers [64-80]. A critical avenue is to investigate the crosstalk between ferroptosis and other RCD pathways, especially PANoptosis, during viral infection. Future studies should determine whether the FMI score correlates with a virus's propensity to engage PANoptosis and how combined modulation of multiple death pathways affects viral replication and disease severity. Finally, expanding this systematic approach to other metal-dependent cell death pathways, such as cuproptosis, may yield a more holistic understanding of how viruses orchestrate cellular demise for their own benefit.

Highlights

- FMI classifies viruses by their quantitative ferroptosis modulation strategy.
- Pro-ferroptotic viruses cause tissue damage.
- Anti-ferroptotic viruses promote persistence and cancer.
- Context-dependent viruses adapt across tissues.
- FMI guides precision therapy: inhibitors for lytic disease, inducers for latent infection and cancer.

Ethics Approval and Consent to Participate

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Declaration of Competing Interest

No potential conflict of interest was reported by the author.

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Data Availability

This is a narrative review article. No new data were created or analyzed in this study.

Conflict of Interest

The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Bahman Aghcheli. Biomed J Sci & Tech Res

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