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Circulating biomarkers of ferroptosis: A new frontier in the diagnosis and biological monitoring of cardiovascular and neurodegenerative diseases

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Abstract

Ferroptosis is defined as a novel pathway of regulated, iron-dependent cell death. It relies on three main metabolic pathways: iron metabolism, lipid peroxidation, and the GSH/GPX4 antioxidant system. Several studies have shown that this cell death process is implicated in the pathophysiology of numerous chronic diseases, particularly cardiovascular diseases (myocardial infarction, heart failure, cardiomyopathy, ischemia-reperfusion injury) and neurodegenerative disorders (Parkinson's disease, Alzheimer's disease, etc.). Circulating biomarkers of ferroptosis—such as MDA, 4-HNE, isoprostanes, oxidized phospholipids, GPX4, and GSH, as well as markers of iron metabolism—represent promising diagnostic and prognostic tools that could revolutionize the management of patients with these conditions. However, further efforts are required before these parameters can be adopted for routine clinical use. The aim of this work is to summarize current knowledge regarding the main circulating biomarkers of ferroptosis and to examine their potential as diagnostic tools for cardiovascular and neurodegenerative diseases.

Keywords: Ferroptosis; Circulating biomarkers; Cardiovascular; Neurodegenerative.

1. Introduction

Cell death can occur via various mechanisms, including apoptosis, necrosis, autophagy, and ferroptosis. The latter was defined by Dixon et al. in 2012 as an iron-dependent, regulated cell death process [1]. It is characterized by the excessive intracellular accumulation of ferrous iron (Fe^{2+}), which promotes lipid peroxidation of membrane polyunsaturated fatty acids (PUFAs)—leading to massive free radical production—and is associated with an imbalance in the antioxidant system (glutathione (GSH) depletion accompanied by the inactivation of glutathione peroxidase 4 (GPX4)), ultimately causing cell destruction [2].

Interest in ferroptosis has steadily grown [3], and numerous scientific publications have demonstrated the involvement of this biochemical process in the pathophysiology of various acute and chronic conditions, such as cardiovascular diseases (heart failure, ischemia-reperfusion injury), neurodegenerative disorders (Parkinson's disease, Alzheimer's disease), inflammatory diseases, infectious diseases, chronic kidney diseases, and certain cancers [4], [5]. Understanding ferroptosis and identifying it as a common mechanism in these and other pathologies has enabled the clinical development of new therapeutic strategies and targets, as well as the biological study of various circulating biomarkers indicative of active ferroptosis.

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In clinical biochemistry, the current challenge lies in defining reliable circulating biomarkers for assessing ferroptosis, determining how and by what technique to measure them, standardizing assay kits, ensuring sample stability, and developing biological scores for cardiovascular and neurodegenerative risk stratification.

Objective

This work aims to present a summary of current knowledge regarding the main circulating biomarkers of ferroptosis and to examine their potential as diagnostic tools for cardiovascular and neurodegenerative diseases.

2. Fundamental biochemical mechanisms

Ferroptosis is a cell death process that relies on three main interconnected metabolic pathways, namely:

2.1. Iron metabolism pathway

Iron is a vital trace element for the body. Several metabolic enzymes require iron as an essential catalytic cofactor for their function (lipoxygenases (LOXs) and NADPH-cytochrome P450 oxidoreductase (POR)) [6]. Furthermore, due to its ability to readily accept or donate electrons, free iron is potentially toxic [7]; intracellular accumulation of Fe^{2+} catalyzes the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\bullet$), thereby generating highly reactive hydroxyl radical species.

2.2. Lipid peroxidation pathway

Membrane phospholipids, particularly phosphatidylethanolamines (PE) containing polyunsaturated fatty acids (PUFAs) such as arachidonic acid (20:4 ω-6) are the primary targets of lipid peroxidation due to the high reactivity of their double bonds [8], [9]. This is a chain reaction that proceeds in three successive phases : initiation, propagation, and termination (Figure 1) [8].

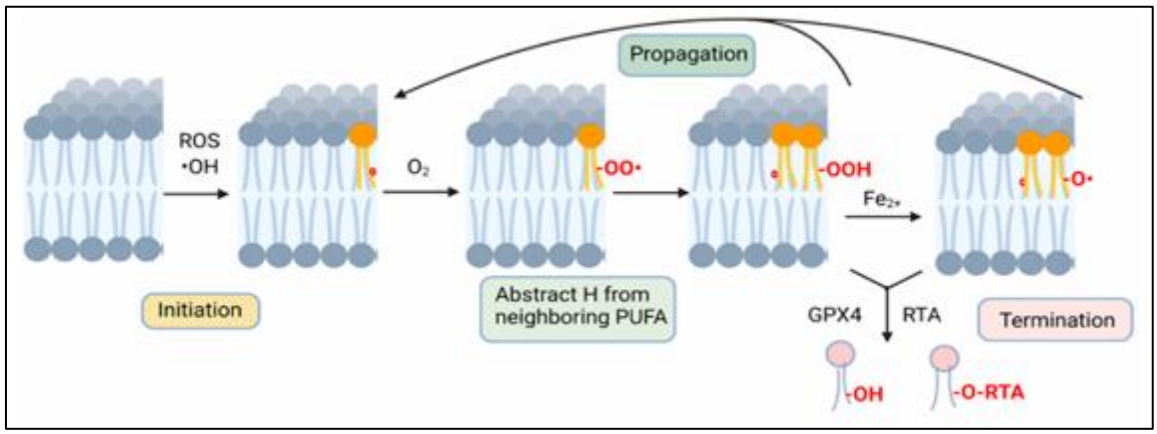

Figure 1 The stages of lipid peroxidation of membrane phospholipids.

2.2.1. Initiation [8], [10]

This step is initiated by the abstraction of a hydrogen atom from the carbon chain of the PUFA by reactive oxygen species (ROS), particularly hydroxyl radicals (OH). This results in an unpaired electron on the lipid molecule, followed by an electronic rearrangement involving the adjacent double bond to achieve a more stable state; this leads to the formation of lipid radicals (L•), which rapidly react with molecular oxygen to generate a lipid peroxyl radical (LOO•).

2.2.2. Propagation

The propagation step begins when the newly formed lipid peroxyl radical (LOO•) abstracts a hydrogen atom from a neighboring membrane PUFA molecule [9], [11]. This results in the formation of a lipid hydroperoxide (LOOH) and a new lipid radical (L•) [9], [12]. The latter repeats the steps of the initiation phase by losing a hydrogen atom in turn, thereby sustaining the chain reaction and promoting the propagation of lipid peroxidation within cell membranes [11], [12]. This cascade is amplified by the Fenton reaction, in which iron acts to decompose lipid hydroperoxides (LOOH) into highly reactive alkoxyl radicals (LO•) according to the reaction: $LOOH + Fe^{2+} \rightarrow LO\bullet + OH^- + Fe^{3+}$ [1], [2], [13].

2.2.3. Termination

This final step involves halting the propagation of radical reactions and neutralizing lipid radicals and hydroperoxides, either through their enzymatic reduction catalyzed by glutathione peroxidase 4 (GPX4) using reduced glutathione (GSH) as a cofactor [14], [15] or via radical-trapping antioxidants (RTAs) such as vitamin E, ferrostatin-1, liproxstatin-1, and ubiquinol (CoQ10) [11], [16], [17].

Remarks: The main bioactive degradation products generated by lipid peroxidation are: malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), isoprostanes (8-iso-PGF2α), and oxidized phospholipids (ox-PL) [12], [18].

2.3. GSH/GPX4 antioxidant system pathway

The glutathione (GSH)/glutathione peroxidase 4 (GPX4) antioxidant system constitutes the primary defense mechanism against ferroptosis. The key enzyme GPX4, acting in concert with its essential cofactor (glutathione), reduces lipid hydroperoxides (PLOOH) to non-toxic lipid alcohols (PLOH) via the reaction PLOOH + 2GSH → PLOH + GSSG + H_2O; this process prevents the accumulation of lipid peroxidation products and preserves cell membrane integrity. Conversely, glutathione depletion and/or GPX4 inhibition leads to an excessive accumulation of these products, thereby promoting the propagation phase of lipid peroxidation and, consequently, ferroptosis [12], [17].

3. Circulating biomarkers of ferroptosis

3.1. Classification and overview

Table 1 Main circulating biomarkers of ferroptosis.

Category	Biomarker	Matrix	Assay method	Remarks
Iron metabolism	Serum iron	Serum	Colorimetry	Non-specific: Indicate iron overload or dysregulation of iron metabolism, promoting ferroptosis.
	Ferritin	Serum	Immunoturbidimetry	
	Hepcidin	Plasma	ELISA, LC-MS/MS	
	Soluble TfR1 (sTfR)	Serum	ELISA	
Lipid peroxidation	MDA (Malondialdehyde)	Plasma/Serum	TBARS, HPLC	Non-specific: End products of PUFA peroxidation; directly reflect lipid oxidative stress.
	4-HNE (4-Hydroxynonenal)	Plasma	ELISA, LC-MS/MS	
	8-iso-PGF2α (Isoprostanes)	Urine/plasma	GC-MS, ELISA	
	PTGS2 / COX-2	Plasma	ELISA	Non-specific: Reflects massive cell lysis or inflammation.
Antioxidant system	GPX4	Serum/Plasma	ELISA, Western Blot	Markers of cellular antioxidant capacity, the decline of which promotes ferroptosis.
	GSH (Reduced glutathione)	Whole blood	Enzyme assay (DTNB)	
	Soluble SLC7A11	Plasma	ELISA	
Emerging biomarkers	Oxidized phospholipids (ox-PL)	Plasma	LC-MS/MS	New biomarkers, often linked to transcriptional regulation
	Prostaglandins E2 (PGE2)	Plasma/urine	ELISA	

Circulating biomarkers for ferroptosis remain a challenge. Several scientific studies have discussed various markers, but to date, none is valid as a specific parameter for the direct diagnosis of ferroptosis [6]. Furthermore, they can be

classified according to their metabolic pathway into four main categories, summarized in the following table [2], [4], [6]:

3.2. Markers of iron metabolism

Intracellular iron accumulation is the primary trigger for ferroptosis: it catalyzes the Fenton reaction, thereby amplifying lipid peroxidation. In clinical practice, circulating biomarkers of iron metabolism serve as indirect markers of ferroptosis that are readily accessible. They must be interpreted within the overall clinical and inflammatory context, given the numerous factors influencing their circulating levels, such as acute inflammation, hemolysis, and liver disease [6], [7]. The table below summarizes the key markers of this metabolic pathway, their roles in ferroptosis, and the expected variations.

Table 2 Iron metabolism biomarkers.

Biomarker	Role in ferroptosis	Expected variation
Serum iron	Pro-ferroptotic labile iron pool	↑
Serum ferritin	Release of Fe^{2+} via ferritinophagy by ferroptotic cells + acute-phase reaction	↑↑
Transferrin	Transport of Fe^{3+} to cells	↓
Transferrin saturation (CST)	Increased iron uptake by cells	↑
Plasma hepcidin	Blocks ferroportin (FPN) → Intracellular Fe^{2+} ↑	↑ (inflammatory response)
sTfR (soluble receptor)	Increased cellular iron demand	Variable

3.3. Markers of lipid peroxidation

3.3.1. Malondialdehyde (MDA)

Malondialdehyde (MDA) is the most abundant degradation product of PUFA peroxidation. It is the most widely used biomarker for lipid oxidative stress in clinical practice [12], [19]. Several assay techniques are available: the colorimetric TBARS (Thiobarbituric Acid Reactive Substances) method, HPLC (the gold standard), the confirmatory LC-MS/MS (liquid chromatography-tandem mass spectrometry) method, and the ELISA immunoassay [19], [20]. Plasma MDA levels normally range from 0.5 to 2.0 µmol/L and rise significantly in pathologies associated with ferroptosis, thereby reflecting the intensity of overall membrane lipid peroxidation [9], [12]. However, its specificity for ferroptosis remains moderate, as levels also increase in any process involving lipid oxidative stress, regardless of the underlying cell death mechanism [2], [9]. Consequently, this parameter should always be combined with other biomarkers such as 4-hydroxynonenal (4-HNE) and isoprostanes to improve diagnostic specificity for ferroptosis and confirm the presence of oxidative stress [2], [6].

Table 3 Main interferences in the MDA assay.

Interference	Effect	Mechanism
Hemolysis	↑ falsely	Release of erythrocyte MDA
Bilirubin	Variable	Absorbs at 532 nm
Glucose	↑ falsely	Reacts with TBA
Uric acid	↑ falsely	Reacts with TBA
Amino acids	↑ falsely	Reacts with TBA
Vitamin C	↓ falsely	Complex-reducing agent

MDA measurement remains unstandardized despite decades of use. It should be noted that this biomarker is subject to several limitations: issues with result reproducibility, the lack of an international consensus on normal values, and the absence of a universal reference method …[19], [20].

Measuring this biomarker also requires rigorous pre-analytical conditions to avoid analytical interference and ensure the reliability of the results [19], [20]

3.3.2. 4-Hydroxynonenal (4-HNE) [12], [18], [21]

4-Hydroxynonenal (4-HNE) is also a product of the peroxidation of ω-6 PUFAs (linoleic acid and arachidonic acid). Measuring plasma levels of this biomarker using ELISA (the most common routine method) or LC-MS/MS (a sensitive and specific technique) reflects the intensity of oxidative stress and thus serves as an indirect indicator of ferroptosis. However, it is not specific to this type of cell death; consequently, it must be assessed alongside other lipid peroxidation biomarkers, and the overall results must be interpreted within a clearly defined clinical context. There are no universal reference values for this parameter, though some studies cite a normal plasma level of less than 0.1 µmol/L.

4-HNE is considered a highly reactive aldehyde; it rapidly binds to plasma proteins (albumin, apolipoproteins) via covalent bonding, resulting in a reduction of the measurable free fraction and, consequently, an underestimation of its value. The table below lists the main analytical interferences that can affect the measurement of this biomarker [19], [20]:

Table 4 Main interferences in the 4-HNE assay.

Interference	**Effect**	**Mechanism**
Hemolysis	↑ falsely	Erythrocyte 4-HNE release
Plasma proteins	↓ falsely	4-HNE-protein covalent linkage
Albumin	↓ falsely	Rapid uptake of free 4-HNE
Aldehyde based drugs	↑ falsely	Antibody cross-reactivity
Acidic pH	Variable	Instability of 4-HNE
Ambient temperature	↓ falsely	Rapid degradation
Diet (Fasting recommended)	↑ falsely	Diet rich in omega-6

3.3.3. Isoprostanes (8-iso-PGF2α)

Isoprostanes are prostanoids formed through the non-enzymatic peroxidation of esterified arachidonic acid, driven by free radicals. Following their formation, these compounds are released from the cell membrane by the action of phospholipases and enter the bloodstream before being excreted in urine as free isoprostanes (their plasma half-life is generally short). F2-isoprostanes and specifically 8-iso-prostaglandin F2α (8-iso-PGF2α) have been the most extensively studied; due to their high chemical stability, they are currently considered among the most reliable and precise biomarkers for oxidative stress and in vivo lipid peroxidation. Several analytical techniques are available for their quantification, notably gas chromatography-mass spectrometry (GC-MS), liquid chromatography-tandem mass spectrometry (LC-MS/MS)—considered the gold standard—and certain immunological methods (ELISA), although the latter are less specific. The biological matrices most used for measuring these isoprostanes are plasma and, above all, urine ; urinary analysis offers good analytical stability and correlates closely with the severity of oxidative stress. The table below summarizes the advantages and limitations of measuring these biomarkers [20]:

Table 5 Advantages and limitations of isoprostane (8-iso-PGF2α) measurement.

Advantages	limitations
- High stability. - High specificity. - Absence of significant circadian variation. - No influence of diet. - Good correlation with the severity of oxidative stress.	- Technically complex dosing. - Highly qualified personnel. - Short plasma half-life, thereby limiting their use in clinical practice. - Expensive. - Cross-reactivity and inter-kit variability for ELISA/RIA techniques. - Potential auto-oxidation of samples, requiring rigorous sampling and storage conditions.

3.4. Markers of the GPX4/GSH antioxidant system

GPX4 (glutathione peroxidase 4) and GSH (reduced glutathione) constitute the pivotal antioxidant system in ferroptosis. Their depletion represents the central biochemical event triggering ferroptosis-dependent cell death. Consequently, measuring their circulating levels provides a direct diagnostic window into ferroptosis activation [14], [15].

3.4.1. GPX4 (glutathione peroxidase 4)

GPX4 (glutathione peroxidase 4) is a monomeric selenoprotein; it serves as a pivotal cytosolic enzyme in the regulation of ferroptosis due to its ability to directly reduce phospholipid hydroperoxides (PLOOH) to their corresponding non-toxic alcohols (PLOH), using GSH as a cofactor [22]. GPX4 is of significant interest in the context of various pathologies, as a decrease in its plasma activity correlates with the risk of ferroptosis activation [23]. Measurement can be performed either via immunological techniques (ELISA) or by assessing enzymatic activity using spectrophotometry. However, standardization of this assay is required for routine clinical use [6], [23].

3.4.2. Reduced glutathione (GSH) [24], [25]

Reduced glutathione (L-γ-glutamyl-L-cysteinyl-glycine or GSH) is a thiol-containing tripeptide that serves as the primary intracellular antioxidant. GSH depletion is an early and pivotal event in the process of ferroptosis. Numerous studies have established a link between disruptions in GSH metabolism and various conditions, including cancer, neurodegenerative diseases, cystic fibrosis, HIV infection, and aging. Its quantification relies on enzymatic methods using the DTNB reagent also known as Ellman's reagent (5,5'-dithiobis(2-nitrobenzoic acid)) or on HPLC or LC-MS/MS. Its main limitation is its pre-analytical instability, which necessitates strict sampling and storage conditions [25].

Table 6 Main interferences in the assay of reduced glutathione.

Interference	Effect	Mechanism
Hemolysis	↑ falsely	Erythrocyte GSH release
Processing time	↓ falsely	Oxidation of GSH to GSSG
Ambient temperature	↓ falsely	Spontaneous oxidation
Selenium deficiency	↓ indirectly	↓ GPX4 → ↑ consumption GSH

Analytical challenges and current limitations

- Lack of specificity of certain biomarkers (MDA, GSH) for ferroptosis compared to other forms of cell death.
- Pre-analytical instability of redox biomarkers, requiring strict conditions for collection, processing, and storage.
- Absence of standardized reference values and harmonized assay methods across laboratories.
- Lack of multi-biomarker panels combining markers of lipid peroxidation, the antioxidant system, and iron metabolism for improved diagnostic specificity of ferroptosis.
- Unavailability of the majority of these assays in routine clinical practice.
- Need to develop biological scores for cardiovascular and neurodegenerative risk stratification to ensure better interpretation of results.

Ferroptosis and cardiovascular diseases

Iron is an essential trace element in numerous biological processes, such as energy metabolism, DNA synthesis and repair, and various enzymatic reactions [7]. In humans, iron deficiency is the most common form of deficiency, affecting up to 75% of patients with heart failure [26]. Conversely, iron overload (whether primary or secondary) promotes the development of cardiac pathologies through mechanisms involving oxidative stress [27]. It has been demonstrated that excess intracellular iron in cardiomyocytes directly induces ferroptosis by promoting the accumulation of phospholipid hydroperoxides in cell membranes [28]. In addition to disruptions in iron homeostasis, the excessive production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) can also trigger ferroptosis by catalyzing the oxidation of membrane phospholipids. In this regard, bolstering cellular antioxidant systems particularly the glutathione/GPX4 pathway has been shown to prevent cardiomyopathy in several experimental models [29], [30]. Indeed, numerous studies have demonstrated that ferroptosis plays a major role in the development of various cardiovascular conditions, including cardiomyopathies, myocardial ischemia-reperfusion injury, myocardial infarction, and heart failure [1], [31]. Growing understanding of the pathophysiological mechanisms of ferroptosis and their involvement in cardiovascular disease underscores the value of investigating circulating ferroptosis biomarkers and highlights the need for a multiparametric approach; combining conventional cardiac markers (high-sensitivity troponin I/T, BNP/NT-proBNP, CK-MB) with circulating ferroptosis biomarkers (GPX4, MDA, 4-HNE, isoprostanes, and ox-PL) could help improve the diagnosis, risk stratification, and monitoring of patients with cardiovascular disease.

The table below summarizes the clinical relevance of ferroptosis biomarkers in certain cardiovascular diseases

Table 7 Clinical significance of ferroptosis biomarkers in certain cardiovascular diseases.

Cardiovascular disease	Ferroptosis biomarker	Variation	Clinical benefit
Myocardial infarction	MDA, 4-HNE plasma	↑↑	Prognosis (Necrosis size)
Heart failure	GPX4 serum, GSH	↓↓	Diagnosis – severity
Cardiomyopathy	Ferritin, serum iron	↑	Therapeutic monitoring
Ischemia-reperfusion	Urinary isoprostanes	↑↑	Early reperfusion injury
Atherosclerosis	Oxidized phospholipids (ox-PL)	↑	Cardiovascular risk

4. Ferroptosis and neurodegenerative diseases

Ferroptosis is recognized as a major player in the pathophysiology of neurodegenerative diseases, notably Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [32], [33]. These conditions represent a major public health challenge, with prevalence increasing alongside aging. For instance, approximately one in ten people aged 65 or older suffers from Alzheimer's disease (AD) [34], an irreversible condition that, to date, lacks a curative treatment [35], [36].

Iron is essential for meeting the high metabolic demands of nervous tissue. It plays a key role in myelination, neuronal energy metabolism, and the synthesis of several neurotransmitters (dopamine and noradrenaline) [37]. However, numerous studies have shown that excessive iron accumulation in brain tissue impairs cerebral function due to its redox properties; it catalyzes the formation of reactive oxygen species (ROS), thereby promoting intracellular oxidative stress, lipid peroxidation, and oxidative damage that causes astrocyte injury, thus contributing to the development and progression of neurodegenerative diseases [37].

In Alzheimer's disease, several studies have reported a significant increase in MDA and 4-HNE levels in the cerebrospinal fluid (CSF) and plasma of affected patients, correlating with the severity of cognitive impairment as assessed by the MMSE (Mini-Mental State Examination) score [38], [39]. Furthermore, reduced plasma GPX4 activity and lower erythrocyte GSH levels have been observed in these patients, suggesting the activation of neuronal ferroptosis [38]. Elevated urinary isoprostane (8-iso-PGF2α) levels also serve as a circulating biomarker reflecting the intensity of lipid peroxidation [20], [39].

In Parkinson's disease, elevated serum iron and plasma ferritin levels—associated with decreased circulating GPX4 and GSH—have been reported in patients; this biological profile closely aligns with the biochemical characteristics of

ferroptosis [40], [41]. Measuring other circulating ferroptosis biomarkers, such as urinary isoprostanes and plasma 4-HNE, also serves as a non-invasive tool for monitoring lipid peroxidation in this condition [20], [39].

In amyotrophic lateral sclerosis, elevated levels of urinary isoprostanes (8-iso-PGF2α) and plasma MDA have been observed in patients with the disease. A decrease in the erythrocyte GSH/GSSG ratio also serves as an accessible circulating biomarker reflecting the glutathione depletion associated with motor neuron ferroptosis [38].

The involvement of ferroptosis in the aforementioned neurodegenerative diseases as well as others suggests that circulating ferroptosis biomarkers (GPX4, GSH, MDA, 4-HNE, isoprostanes, and iron metabolism markers) could serve as diagnostic and prognostic tools complementing the conventional biomarkers used for neurodegenerative diseases. However, further efforts are required before these parameters can be adopted for routine clinical use.

5. Conclusion

Ferroptosis is defined as a novel pathway of regulated, iron-dependent cell death. It is implicated in the pathophysiology of numerous chronic diseases, notably cardiovascular and neurodegenerative disorders, which represent a global public health challenge and a significant burden of morbidity and economic cost [6], [42].

Circulating biomarkers of ferroptosis—categorized into markers of lipid peroxidation (MDA, 4-HNE, isoprostanes, ox-PL), antioxidant system markers (GPX4, GSH), and iron metabolism markers (iron, ferritin, hepcidin, sTfR1)—represent promising diagnostic and prognostic tools for cardiovascular and neurodegenerative diseases [20]. Integrating them alongside conventional biomarkers within a multiparametric approach could significantly improve risk stratification and therapeutic management for patients with these conditions [2], [43]. However, major obstacles to their use include the lack of specificity of these markers, the absence of analytical standardization, a lack of clinical studies, reference values, and decision thresholds validated in well-defined populations, as well as the unavailability of most of these assays in routine clinical practice.

In conclusion, circulating biomarkers of ferroptosis clearly represent a promising new diagnostic and therapeutic frontier in cardiovascular and neurodegenerative diseases. Addressing the associated challenges and accelerating their adoption into routine clinical practice—which could revolutionize the management of these conditions—requires close collaboration among medical biologists, clinicians, and researchers from both academia and industry [2], [6], [42].

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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