ARTICLE

The Sepsis-Ferroptosis Axis: Identifying the Regulatory Role of Hub Genes Networks in Cellular Dysfunction

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Abstract

Background: *Sepsis is a serious, life-threatening condition caused by a dysregulated host response to infection, frequently leading to multi-organ dysfunction, high morbidity, and mortality worldwide. Despite innovations in medical care, it continues to pose a significant global health burden. Regulated cell death pathways, particularly ferroptosis, have been identified as a major factor in sepsis-induced organ damage.*

Methods: *In this study, the RNA-Seq dataset GSE154918 was analyzed to identify ferroptosis-related differentially expressed genes (DEGs) in sepsis patients, while the RNA-Seq dataset GSE185263 was used for results validation. Protein–protein interaction networks were created using STRING and depicted in Cytoscape, with hub genes identified through the CytoHubba MCC algorithm.*

Results: *A systematically compiled list of 2,083 human ferroptosis-related genes from FerrDb V3 was intersected with DEGs, resulting in 394 ferroptosis-associated candidates. Functional annotation analyses (GO and KEGG) indicated that these hub genes are involved in cell cycle regulation, p53 signaling, and mitotic checkpoint pathways. Consistent downregulation of key hub genes such as CDK1, AURKA, AURKB, CDC20, PLK1, TOP2A, RRM2, BUB1, NEK2, and BIRC5 were found during validation across datasets, suggesting their vital role in ferroptosis-induced pathology.*

Conclusion: *These outcomes endorsed that the hub genes stand as a promising biomarker for sepsis. Furthermore, this also confirms the significant role of ferroptosis in sepsis. Modulating ferroptosis via pharmacological inhibitors or gene-targeted interventions may offer a prospective approach to attenuate organ injury and ameliorate clinical consequences in septic patients.*

Key words: *CytoHubba, Ferroptosis, GO, Hub genes, KEGG, STRIGN db*

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Competing interests
The authors have declared that no competing interests exist.

Introduction

Despite advancements in medical care, Sepsis, which is a fatal disease, remained a global health burden with high rates of morbidity, organ dysfunction, and economic burden (Markwart et al., 2020; La Via et al., 2024). Although it is difficult to ascertain the accurate measure of global epidemiological load, recent scientific literature showed that sepsis causes 11 million deaths and influences approximately 49 million people worldwide. It is also seen in developed and developing countries, where the ratio is higher, with over 48 million cases per year (Cassini et al., 2020; Markwart et al., 2020). Although it is a serious issue in the realm of health, the data for measuring global burden and proportion are limited and unclear due to hospital-acquired infections (Markwart et al., 2020).

The recent definition of sepsis is incomplete as it is unable to capture the complex pathogenicity of sepsis and is characterized by simultaneous dysregulation of immune suppression and hyperinflammation (van der Poll et al., 2021). This persistent immune suppression promotes oxidative stress, inducing direct cellular and tissue injury. It eventually results in impairment of the organ system (Vella et al., 2025). Organ dysfunction in sepsis is directly caused by necroptosis, apoptosis, autophagy, and pyroptosis (Wang et al., 2025). The mechanisms of regulated cell death (RCD) have garnered more focus because these dying cells release numerous stress stimuli that help in providing an early diagnosis and a treatment strategy (Qu et al., 2022).

Ferroptosis, a form of regulated cell death, is dependent on iron and reactive oxygen species

(ROS), characterized by lipid peroxidation and grows in the accumulation of ROS in the form of lipid hydroperoxides (Latunde-Dada, 2017). Apoptosis and necrosis are mechanistically and morphologically divergent from ferroptosis, which has recently emerged as an exceptional, iron-mediated programmed cell death (Artusi, 2025). Additionally, accumulating evidence suggest the involvement of ferroptosis in various morbid conditions such as degenerative neurological disorders, cancer, cardiovascular diseases, sepsis, ischemia-reperfusion injury, and metabolic disorders (Chen et al., 2024; Yu et al., 2021).

Recent evidence indicates the significance of ferroptosis in sepsis occurrence and development (Liu et al., 2022). Sepsis is associated with elevated oxidative stress, mitochondrial dysfunction, disrupted iron homeostasis, and lipid peroxidation, hallmark processes that promote ferroptotic cell death. Experimental evidence suggests the systemic interaction of ferroptosis with sepsis-associated immune cell damage, suppression, aberrant regulation of the immune system, and in sepsis-mediated multi-organ injury, such as acute lung injury, acute renal injury, septic cardiomyopathy, and encephalopathy (H. T. Zhou et al., 2025). Similarly, inhibiting ferroptosis pharmacologically significantly alleviates cardiac injury, proinflammatory cytokine production, and improves survival rate in a sepsis-induced mouse model, and it also highlights that targeting ferroptosis may provide a new therapeutic strategy in sepsis (Xl et al., 2022; H. T. Zhou et al., 2025).

Limited information is available on ferroptosis and its relationship with sepsis. Current studies in this field mainly focus on regulatory networks and enrichment pathways, along with their involvement in oxidant and antioxidant systems. Meanwhile, novel strategies targeting ferroptosis in the field of radiotherapy and immunotherapy are still insufficient (Cheng et al., 2022). Previous studies have particularly identified significant DEGs, hub genes, and enrichment pathways retrieved for these hub genes, which tend to provide novel therapeutic intervention and diagnostic prediction (Heydari et al., 2025). Bioinformatic analysis and high-throughput sequencing technology can lead to a breakthrough regarding immunity related mechanisms and pave the way for biomarker discovery (ShilinLi & Hu, 2024; Taha et al., 2025).

Thus, in this research work, Geo2R analysis of RNA-Seq data and bioinformatic strategies were used to address the ongoing void in the transcriptomic framework, identifying significant DEGs, visualizing different plots, and ferroptosis-related hub genes associated with sepsis.

Besides gene retrieval, protein-protein interaction was studied. Additionally, to have accurate attribution of ferroptosis and sepsis, Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomics (KEGG) pathways, and functional enrichment analysis were utilized. Resultantly, the dual dataset approach supported us to discover novel biomarkers and potential therapeutic agents for subsequent medical intervention in subjects suffering from sepsis.

Methods

Data acquisition and pre-processing using GEO2R

RNA-Seq datasets of sepsis were obtained from Gene Expression Omnibus (GEO). We used two datasets: GSE154918 (Herwanto et al., 2021) as the discovery dataset and GSE185263 (Baghela et al., 2022) as the validation dataset. GPL20301 platform (Illumina HiSeq 4000, *Homo sapiens*) was used to obtain discovery dataset. It had 105 samples, out of which 40 healthy samples were defined as the control group and 20 sepsis patients as the experimental group. To retrieve the validation dataset, the GPL16791 platform (Illumina HiSeq 2500, *Homo sapiens*) was accessed. In this dataset, total number of samples were 392, with 44 healthy samples designated as the control group and 348 sepsis patients were designated as the experiment group.

Differential gene expression analysis was executed using GEO2R, with normalization and log2 transformation applied to the discovery dataset. To validate the robustness of the findings, a consistent analysis pipeline was implemented for the validation cohort, utilizing the same cutoff thresholds to identify differentially expressed genes (DEGs) defined as $|\log_2$ fold change$| > 1$ and p-value < 0.05.

Table 1: RNA-Seq datasets of Sepsis under study

Datasets	Platform	Total Samples	Sepsis	Healthy
GSE154918	GPL20301	105	20	40
GSE185263	GPL16791	392	348	44

Ferroptosis-related genes retrieval from FerrDb and intersection analysis via Venny

Ferroptosis related genes were obtained from FerrDb V3 (N. Zhou et al., 2025), a comprehensive database of experimentally validated and predicted ferroptosis regulators. Three categories of genes: driver, suppressor, and marker, were downloaded and subsequently filtered to include only human-specific genes. A non-redundant set of 2083 human ferroptosis-related genes was obtained by combining the three gene lists and removing duplicate entries. The curated ferroptosis gene was intersected with the significantly differentially expressed genes (DEGs) from both discovery and validation datasets to find potential ferroptosis-related genes linked to sepsis. Venny 2.1.0 (Oliveros, 2007) was used to perform intersection analysis. The overlapping genes were visualized using a Venn diagram, facilitating the identification of anticipated ferroptosis-associated DEGs for downstream analysis.

PPI network construction using STRING and hub genes identification from Cytoscape

To investigate the functional relationships among the candidate genes, a protein-protein interaction (PPI) network was built using the overlapping ferroptosis-related DEGs. To identify interactions, the STRING database V12 (Szklarczyk et al., 2023) was used with a medium confidence score threshold of 0.4. The resulting PPI network was imported into Cytoscape V3.10.4 (Shannon et al., 2003), where network visualization was performed. The CytoHubba plugin was then used to calculate and visualize the top 10 nodes. The Maximal Clique Centrality (MCC) method was applied to rank nodes for downstream functional enrichment analysis and biological interpretation.

Functional enrichment analysis using Enrichr

The top 10 hub genes annotated by the CytoHubba MCC method were subjected to functional enrichment analysis using Enrichr. Gene Ontology (GO) analysis identified the associated biological processes (BP), cellular components (CC), and molecular functions (MF). Moreover, KEGG (Kyoto Encyclopedia of Genes and Genomes pathway) enrichment was performed to identify key signaling and metabolic pathways in which these hub genes are involved.

Validation of Hub genes across both datasets

The expression profiles of the top 10 genes were compared between the discovery (GSE154918) and validation (GSE185263) datasets to verify the reliability of the identified hub genes. Genes that exhibited comparable patterns across both datasets were considered consistently linked to sepsis.

Results

DEGs and Ferroptosis-related genes identification

Two RNA-seq datasets, GSE154918 and GSE185263, were processed via GEO2R, an online tool that uses the DESeq2 R package. In the discovery dataset (GSE154918), differentially expressed genes (DEGs) were identified using a cutoff of $|\log_2 \text{fold change}| > 1.0$ and a p-value < 0.05. A total of 1,847 up-regulated genes and 2,658 down-regulated genes were identified in the discovery cohort and shown as Volcano and bar plot (Figure 1A, & 1B). The validation dataset, GSE185263, was analyzed using the same criteria, and the analysis revealed 925 up-regulated genes and 2,611 down-regulated genes with $|\log_2 \text{fold change}| > 1.0$ and p-value < 0.05 (Figure 1C, & 1D).

A total of 2,083 ferroptosis-related genes, including driver, suppressor, and inducer genes, were retrieved from the FerrDb V3. A Venn diagram demonstrates the overlap between DEGs from the discovery dataset and ferroptosis-related genes. Ultimately, 394 overlapping genes were identified and considered as potential ferroptosis-related biomarker candidates (Figure 2).

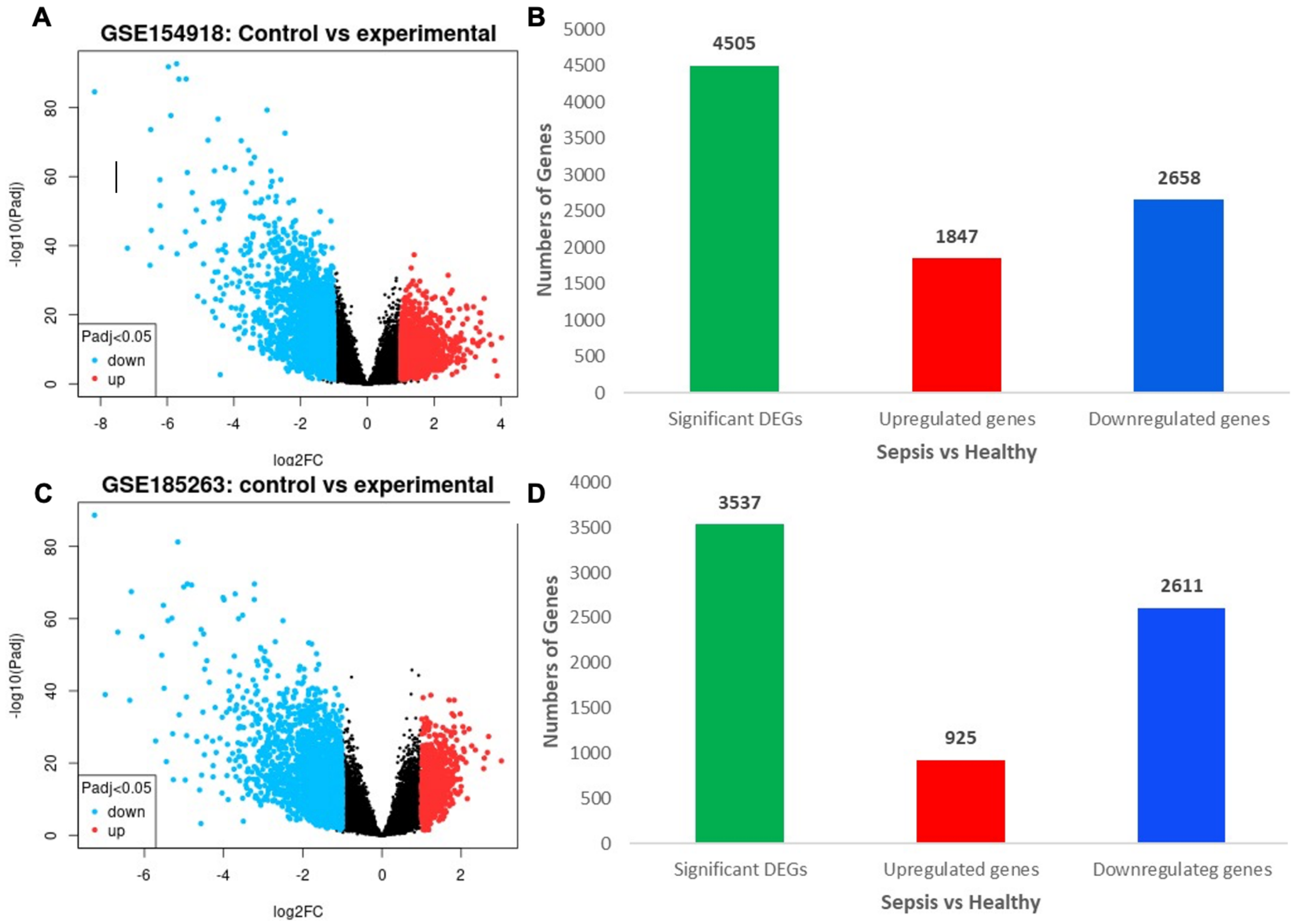

Figure 1: DEGs and Ferroptosis-associated genes identification. (A,B) Volcano plot and bar plot of Sepsis Patients vs Controls in discovery dataset GSE154918. (C,D) Volcano and plot of Sepsis patiients vs Controls in validation dataset GSE185263.

Construction of the PPI network and hub genes confirmation

The 394 overlapping ferroptosis-related genes were categorized by intersecting them with driver, suppressor, and marker gene lists. Among these, 183 genes were classified as driver, 258 as suppressor, and 8 as marker. To explore protein-protein interactions (PPI) among these genes, the STRING database was used to construct a PPI network, which included 383 nodes and 2,874 edges, with an average node degree of 15, and a PPI enrichment p-value < 1.0e-16. The network was subsequently visualized using Cytoscape V3.10.4. The CytoHubba plugin, applying the MCC method, ranked and selected the top 10 nodes. The identified hub genes included CDK1, AURKA, AURKB, CDC20, PLK1, TOP2A, RRM2, BUB1, NEK2, and BIRC5 (Figure 3). These hub genes were further categorized by intersecting with the ferroptosis driver, suppressor, and marker gene lists. Of the 10 hub genes, 3 were driver, 9 were suppressor, and none were marker (Table 2). This analysis highlights key ferroptosis-related hub genes that may serve as potential biomarkers or therapeutic targets in sepsis.

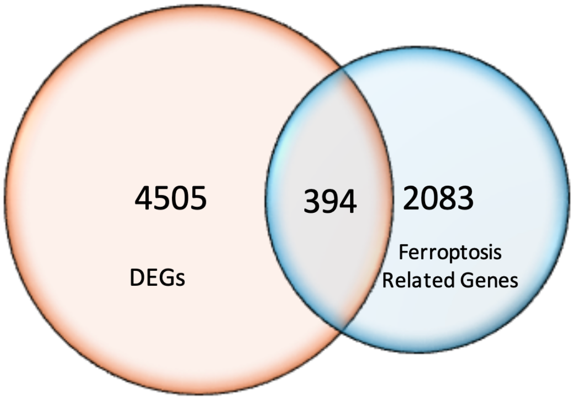

Figure 2: Venn diagram showing common genes between DEGs of discovery dataset and ferroptosis-related genes.

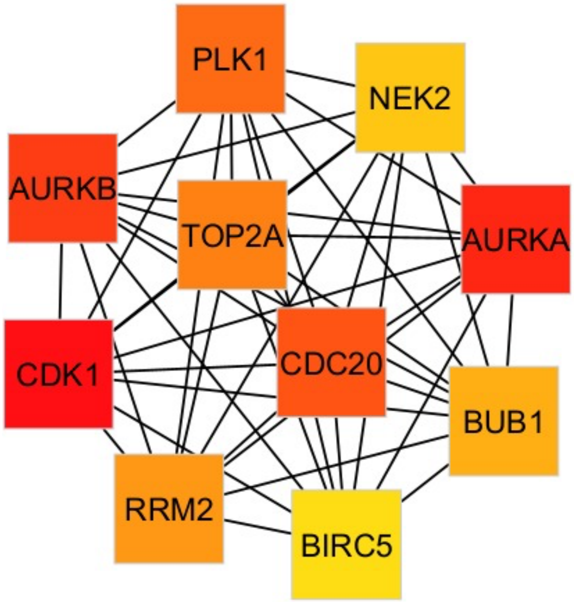

Figure 3: The top 10 Hub genes ranked using CytoHubba (MCC method). Cytoscape visualization of top 10 Hub genes. The network includes 383 nodes, 2874 edges, with an avg node degree of 15, and PPI enrichment p-value < 1.0^{-16}.

Table 2: Top 10 Ferroptosis-related DEGs; 3 genes are driver, 9 are suppressor, and none are marker.

Category	Abbreviated	Name of Gene
Driver	RRM2	Ribonucleotide Reductase
	CDK1	Cyclin-dependent kinase 1
	TOP2A	Topoisomerase IIα
Suppressor	RRM2	Ribonucleotide Reductase
	AURKA	Aurora Kinase A
	NEK2	NIMA-related kinase 2
	BUB1	Budding Uninhibited by Benzimidazole 1
	CDC20	Cell Division Cycle 20
	PLK1	Polo-like kinase 1
	BIRC5	Baculoviral IAP Repeat Containing 5
	AURKB	Aurora Kinase B
	CDK1	Cyclin-dependent kinase 1
Marker	-	-

GO and KEGG enrichment analyses of hub genes

Gene Ontology (GO) and KEGG enrichment analyses were performed for the 10 hub genes using the Enrichr platform, and the top-enriched terms were ranked based on p-values. In the GO Biological Process (BP) category, the most significantly enriched terms included cell cycle G2/M phase transition, mitotic spindle assembly checkpoint signaling, and regulation of mitotic cell cycle. GO Cellular Component (CC) analysis revealed significant enrichment in spindle and microtubule-associated structures, such as spindle microtubule and microtubule cytoskeleton, indicating their involvement in mitotic machinery and chromosomal segregation. Furthermore, in the GO Molecular Function (MF) category, the top enriched terms were protein serine/threonine kinase activity, protein serine/threonine/tyrosine kinase activity, protein heterodimerization activity, and kinase binding, suggesting their role in signal transduction processes governing cell cycle progression (Figure 4).

Additionally, KEGG pathway analysis indicates that hub genes are associated with the regulation of cell cycle, oocyte meiotic division, p53 signaling cascade, progesterone-mediated egg maturation, and virus-induced carcinogenesis.

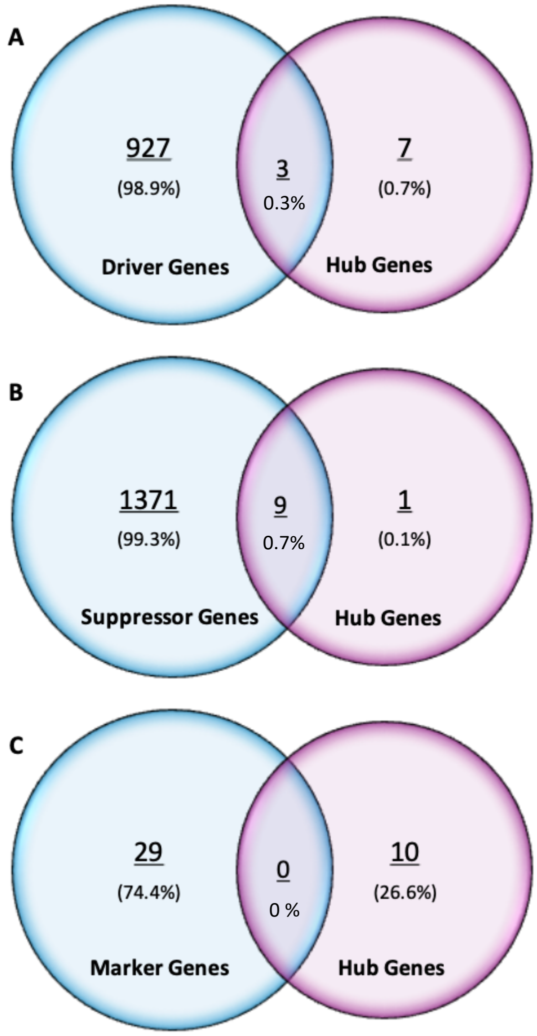

Figure 4: Categorization of Hub genes by intersecting them with Ferroptosis (A) driver (B) suppressor, and (C) marker genes.

In silico validation of hub genes

Subsequently, after identification of the top 10 hub genes, their phenotypic expressions were validated to evaluate their persistence across datasets. Initially, the expression of these genes was examined in the discovery dataset GSE154918, where all 10 genes were found to be downregulated in whole blood samples. To validate these findings, a validation dataset, GSE185263, was used with the same criteria. Notably, despite being generated on a different sequencing platform, the validation dataset confirmed the same expression trends, with all the hub genes remaining markedly downregulated. The reproducibility of these results across datasets derived from distinct platforms highlights the robustness and reliability of the identified genes. The consistent downregulation observed in both datasets strengthens the evidence that these ferroptosis-related hub genes may serve as prognostic biomarkers or potential therapeutic candidates in sepsis, reinforcing their role in ferroptosis-mediated disease mechanisms (Figure 5).

Discussion

Sepsis is a severe clinical condition defined by an unusual host response to infection. It mostly leads to multi-organ dysfunction and high global mortality (Rudd et al., 2020). The term ferroptosis was firsts described by Dixon (Dixon et al., 2012). Growing experimental and clinical evidence suggest that ferroptosis is a key contributor to sepsis-induced organ injury. In terms of sepsis, ferroptosis is characterized by iron accumulation, high lipid peroxidation, and compromised antioxidant capacity, such as inhibition of glutathione peroxidase 4 (GPX4) (Liu et al., 2022). Experimental studies in sepsis-induced ALI provide additional support for the pathogenic role of ferroptosis. For example, it was demonstrated in LPS- and CLP-induced ALI models that dysregulated ferroptosis, along with disturbances in autophagy and pyroptosis, is involved in alveolar epithelial and macrophage injury (Shen et al., 2024). Similarly, pharmacological inhibition of ferroptosis in macrophages reduces lung injury by Nrf2 pathway activation. It highlights the therapeutic relevance of ferroptotic regulation (Zhang et al., 2025).

The outcomes from these investigations endorsed our transcriptomic data, indicating dysregulation of genes attributed to ferroptosis. In present investigation, we executed RNA-Seq analysis to determine ferroptosis-related molecular alterations induced in sepsis. Furthermore, ferroptosis-related differentially expressed genes (DEGs) were identified. PPI analysis retrieved hub genes from DEGs. In both discovery and validation cohorts, our identified ferroptosis-mediated hub genes were down-regulated. The consistent downregulation of hub genes is the main outcome of our study.

These genes play an important role in nucleotide metabolism, DNA replication, mitotic progression, and cell-cycle regulation. This approach enabled us for the identification of coordinated regulatory patterns. It allowed us a network-based interpretation of ferroptosis involvement in sepsis pathophysiology.
Through ferroptosis-linked mechanisms, RRM2 promotes sepsis progression (He et al., 2024). TOP2A is identified as a key regulator in dysregulated gene networks in sepsis-induced ARDS (Ma et al., 2021). RRM2, AURKB, CDK1, and CDC20 have been identified as hub genes with potential therapeutic value in sepsis and its complications Tian et al., 2025; (Vastrad & Vastrad, 2023). The consistent downregulation of these hub genes across both datasets links ferroptosis to impaired DNA and cell-cycle regulation during sepsis. Furthermore, these hub genes may act upon p53-dependent regulatory pathways, which integrate cell cycle arrest and ferroptotic signaling in affected tissues.

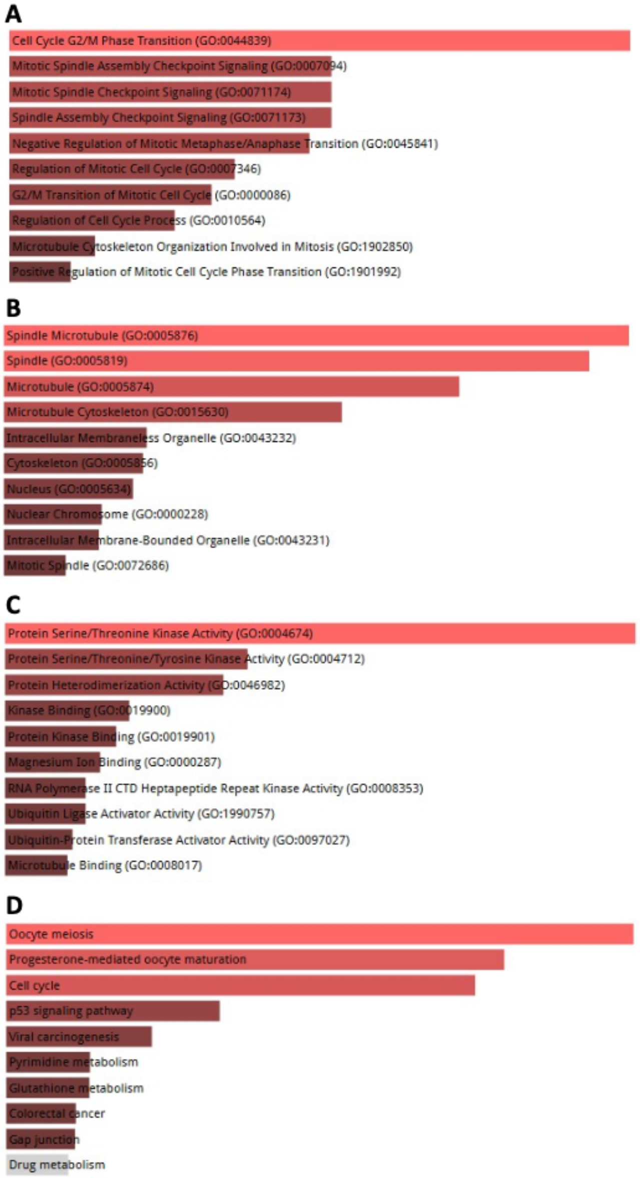

Figure 5: Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses of top 10 Ferroptosis-associated DEGs using Enrichr. (A,B,C) GO-B, GO-CC, and GO-MF enrichment analyses showing enriched terms in top 10 Ferroptosis-related DEGs. (D) KEGG pathway analysis demonstrating enriched terms in top 10 Ferroptosis-related DEGs.

Recent studies show that p53 is a key regulator of ferroptosis in sepsis. The expression of target genes triggered by intracellular and extracellular stressors is regulated by p53 (functioning as a transcriptional regulator). In addition to its transcriptional role, p53 can function independently to regulate ferroptotic signaling. Importantly, several down-regulated hub genes identified in this study are known to intersect with p53-mediated pathways. It points out a direct link between cell-cycle suppression, DNA stress, and increased sensitivity to ferroptosis. The above molecular mechanisms provide important insights into the pathophysiology of sepsis. All these understandings may be beneficial for future outlook and development of new treatments (Gao et al., 2023).

Further biological support for our findings is provided by comparison with already available transcriptomic studies. Reduced expression of genes related to cell proliferation, DNA replication, and mitosis, especially within circulating immune and endothelial cells, is reported by large-scale RNA-Seq analysis of septic patients. Experimental studies also indicate that pharmacological inhibition of ferroptosis reduces organ injury. Suppression of ferroptosis also improves survival in sepsis models, which supports its role in disease. (Shen et al., 2024; Zhang et al., 2025).

From a clinical perspective, these findings show that ferroptosis-related hub genes play a key role in the management and treatment of sepsis and drug development. Ferroptosis contributes to sepsis-induced multi-organ impairment through iron-dependent lipid peroxidation and amplification of inflammatory signaling pathways. Emerging evidence indicates that ferroptosis plays a key role in sepsis progression (Liu et al., 2022; Xl et al., 2022). Previous research studies indicate that iron chelators can prevent ferroptosis in sepsis models, thereby improving survival rate. These findings highlight the importance of iron regulation in the management of sepsis (Liu et al., 2022). Furthermore, inflammation and organ damage are mitigated by ferroptosis inhibitors that provide potential therapeutic strategies for sepsis treatment (Xl et al., 2022). All these results demonstrate that ferroptosis-mediated genes may serve as candidate biomarkers of sepsis. Moreover, these genes play a vital role in sepsis-induced multi-organ injury. Large-scale RNA-Seq datasets with ferroptosis-related genes make our investigation more substantial. It enables targeted analysis of biologically relevant pathways in sepsis. Key regulatory nodes are emphasized by network-based hub gene analysis, increasing clarity. Additionally, validation across independent datasets strengthened the reliability of the analysis. It also links ferroptosis-related gene expression to p53-associated pathways and cell-cycle suppression, which offers new mechanistic insights.

In the present investigation, there are certain limitations as it is based on publicly accessible datasets, which may indicate technical and patient-related variability. Transcriptomic modifications may not precisely reflect protein-level or functional changes. However, this integrative bioinformatics approach provides a solid analytical framework for hypothesis generation and guides future experimental validation.

Conclusion

In conclusion, this study emphasizes the pivotal involvement of ferroptosis in the pathophysiology of sepsis, demonstrating how iron-dependent lipid peroxidation and oxidative stress contribute to immune dysregulation and multi-organ damage. Through integrative transcriptomic and bioinformatics analyses, several ferroptosis-associated hub genes were characterized that showed consistent downregulation across independent datasets, underscoring their potential as robust biomarkers and therapeutic targets. Functional enrichment analyses revealed substantial associations with cell cycle regulation, p53 signaling, and mitotic control, emphasizing their role in ferroptosis-driven tissue injury. Collectively, these findings provide strong support for targeting ferroptotic pathways as a novel anti-inflammatory and organ-protective strategy in sepsis, offering valuable implications for prognostic evaluation and precision medicine. To effectively control ferroptosis in sepsis management, further experimental validation and exploration of combination therapeutic approaches are warranted.

Author contributions

ES, AB, IA, equally contributed from literature search, data mining, data analysis, initial and revised draft preparation. ML guided them regarding analysis tools and compilation and presentation of data and manuscript drafting, NS conceptualized the idea, supervised the work, analysis and writeup.

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