Heliyon 10 (2024) e37617

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Visual analysis on ferroptosis and its cross-talk to coronavirus disease 2019 (COVID-19)

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ARTICLE INFO

Keywords:
Ferroptosis
Citespace
Bibliometric
Visual atlas
COVID-19

ABSTRACT

Background: Ferroptosis is a new type of programmed cell death. Although ferroptosis has been studied in various aspects, there has been no visual analysis of ferroptosis in coronavirus disease 2019 (COVID-19) to date. It is still a global health concern of the COVID-19 pandemic worldwide, three years after its outbreak. Yet the emergence of the mutant strain Omicron has caused a fourth wave of infections in many countries. The pathogenesis of COVID-19 is still undergoing extensive exploration, which holds paramount importance in mitigating future epidemics.

Methods: For this study, CiteSpace 6.2 R4 software was used for bibliometric and visual atlas analysis of ferroptosis-related research, and the Genecards database was used to mine ferroptosis and COVID-19-related genes.

Results: We found increasing studies about ferroptosis. China and the United States have demonstrated robust scientific innovation over recent years, with extensive collaboration between their institutions and authors. Ferroptosis and COVID-19 were seen to have 13 shared genes, which may be new targets for the treatment of COVID-19 in the future. Most of the shared genes are enriched in tumor necrosis factor (TNF) pathways. The majority of those genes are up-regulated under the cellular response to oxidative stress. Genes including Tumour necrosis factor (TNF), RELA proto-oncogene (RELA), Activating transcription factor 4 (ATF4), Cytochrome *b*-245 beta chain (CYBB), Jun proto-oncogene (JUN), Mitogen-activated protein kinase 1 (MAPK1) and Heme oxygenase 1 (HMOX1), maybe a breakthrough for ferroptosis and COVID-19. Whilst previous research has shown there to be a relationship between ferroptosis and COVID-19, the specific role of ferroptosis remained unclear. Our study aimed to analyze the research status of ferroptosis and its relationship with COVID-19, to provide a useful reference for further

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https://doi.org/10.1016/j.heliyon.2024.e37617
Received 20 April 2024; Received in revised form 5 September 2024; Accepted 6 September 2024
Available online 7 September 2024

prevention and treatment of COVID-19. Overall, uncovering the role of ferroptosis in SARS-CoV-2 infection is important for the development of new treatment strategies for COVID-19.

1. Introduction

Ferroptosis represents a novel type of programmed cell death, which is characterized by lipid peroxidation (LPO) accumulation and redox imbalance within the cellular environment [1–3]. It is obviously different from other cell death modalities such as apoptosis and autophagy in cell morphology, genetics, and biochemistry [3]. Iron is essential for the accumulation of LPO and the induction of ferroptosis. Iron metabolism primarily encompasses the transport and storage of iron, with the body sustaining a dynamic equilibrium of iron uptake, storage, and excretion through an intricate regulatory network [4]. Given that iron serves as a cofactor for various metabolic enzymes, low levels of Fe^{2+} is enough to sustain metabolism under physiological conditions. However, due to its redox properties, excess Fe^{2+} within cells can enhance the production and accumulation of reactive oxygen species (ROS) via the Fenton reaction or iron-dependent oxidases, leading to oxidative stress-induced cellular damage and ultimately resulting in ferroptosis [5]. Furthermore, lipid metabolism and amino acid metabolism have also been implicated in the pathogenesis of ferroptosis [3,6,7].

Since Dixon first introduced the concept of ferroptosis in 2012, it has garnered global attention [8]. In recent years, substantial advancements have been made in elucidating the mechanisms of ferroptosis, which have been demonstrated to be intricately linked to tumorigenesis, neurodegenerative disorders, ischemic cerebral perfusion, and pathogen infections [8–10]. The phenomenon of virus-induced ferroptosis and its regulatory role in viral replication has been documented. Studies indicate that various viral infections can disrupt the host cell's antioxidant metabolism, iron transport mechanisms, ROS production, and LPO processes, implying a close association between ferroptosis and viral infection [11–13].

It is still a global health concern of the COVID-19 pandemic worldwide, three years after its outbreak. Patients with COVID-19 infection present with malaise, fever, cough, and dyspnea [14]. Until July 2023, more than 700 million people have been infected with COVID-19 globally, and more than 7 million people have died from the infection [15]. Since 2019, SARS-CoV-2 has undergone a large number of mutations, leading to its evolution and thus the formation of different mutants. The COVID-19 pandemic is far from over and unfortunately, on November 11th, 2021, a variant of COVID-19, Omicron, was detected for the first time in South Africa [16]. Compared with previous SARS-CoV-2 variants, the SARS-CoV-2 omicron variant carries a large number of mutations in the spike protein [17]. The SARS-CoV-2 omicron variant is more transmissible between individuals than other SARS-CoV-2 variants and maybe around 2.8 times more infectious than the delta variant [18]. It is reported that Omicron has been detected in 149 countries, with a large proportion in African countries, probably because less than 10 % of the population in Africa has been vaccinated against Neocrown pneumonia, and so may subsequently be detected in more countries [19,20]. So far, the global proportion of the SARS-CoV-2 Omicron variant exceeds that of other SARS-CoV-2 mutants, with more than 3 million cases, giving it global dominance [17]. Studies have shown that the SARS-CoV-2 Omicron variant caused milder illness in patients, which may also be a lucky thing [21,22]. However, the effectiveness of the COVID-19 vaccine waned over time due to the mutant's stronger ability to escape the immune system [23]. COVID-19 not only threatens the lives of people all over the world but also profoundly affects the economies of countries around the globe. According to International Monetary Fund estimates, the prospects for economic recovery in most countries remain bleak due to the continuing impact of the COVID-19 pandemic [15,24]. For example, Thailand's Gross Domestic Product (GDP) fell by 6.1 % in 2020 and Cambodia lost around $3 billion in tourism revenue in 2020 [25]. Since the outbreak of the COVID-19 pandemic, the scholars at home and abroad have joined the research on COVID-19 [26–28]. Despite extensive global efforts dedicated to investigating COVID-19, our current research on its mechanisms remains in progress. Some studies have found that COVID-19 may have a very important relationship with ferroptosis [29–31]. For example, SARS-CoV-2 significantly suppressed the mRNA expression of GPX4, which is associated with ferroptosis [31]. Some studies have found that iron may be a key factor in the pathogenesis of COVID-19 [32,33]. As the pandemic continues to develop, a clear understanding of the direct relationship between COVID-19 and ferroptosis will be very important for COVID-19 treatment, prevention, and control.

CiteSpace is a bibliometric software that analyses data from a field of the literature and presents the results in a graph to assess future trends [34]. With the increasing number of articles related to ferroptosis, bibliometrics is appropriate to assess and outline ferroptosis-related research. Although ferroptosis was studied in various aspects, there has been no visual analysis of ferroptosis in COVID-19 to date. Therefore, it is especially necessary to study the relationship between ferroptosis and COVID-19.

In this study, we implemented CiteSpace 6.2 R4 software to analyze the domestic and international literature related to ferroptosis, to draw a scientific knowledge map for evaluating the research status of ferroptosis, and to develop a cooperation model between countries, institutions, and authors. At the same time, genes related to ferroptosis and COVID-19 were mined and visualized from the Genecards database, looking for the relationship between ferroptosis and COVID-19. We hope that this study may uncover the association between ferroptosis and SARS-CoV-2 infection in vitro and in vivo.

2. Materials and methods

2.1. Database source

In this study, we chose to conduct a literature search using the Web of Science Core Collection (WoSCC) database, which holds a wide variety of global scholarly information, contains a multitude of high-quality journals [35–37], and is the first established citation

database, dating back to 1990 [38]. The search formula was set to TS = (ferroptosis) and the language was limited to English. The first article on ferroptosis research was published in 2012 [39] and so the retrieval time range was set from 2012 to 2023. There are no restrictions on the type of paper. A total of 11,140 papers (no duplicates) were obtained. The retrieved articles were downloaded in "full record plain text format".

2.2. Research tool

CiteSpace is a citation visualization analysis software tool that provides an effective way to analyze large amounts of data [40]. In this study, we used CiteSpace 6.2 R4 to analyze the literature. The software parametric settings were as follows: the time span selected was 2012–2023 and each time slice was 1 year; selected term sources were title, abstract, author, and keywords; node types were set as institution, and author; and thresholds were applied separately according to the visualization effect.

GeneCards is a software application that retrieves, integrates, and displays gene-centric information on the human genome, which provides immediate insights into the current knowledge about genes and their functions in health and disease [41–44]. We also used the Genecards database to mine genes related to ferroptosis and COVID-19, with a relevance score >1, and protein-coding-related genes.

Microsoft Office Excel 2019 was used to manage the database and analyze the trend of the number of articles published each year.

3. Results

Bibliometrics are widely used in various fields. Quantitative analysis of literature through mathematical and statistical methods can not only obtain some important information on the subject at hand but may also predict the future development and direction of the field. This trial systematically summarised the studies on ferroptosis since 2012, revealing the current state of research. Since the discovery of ferroptosis more and more publications have appeared, especially in China. Collaboration analysis showed limited partnerships between countries, institutions, and authors. At the same time, this experiment analyzed the genes related to ferroptosis and COVID-19 to look for a relationship between ferroptosis and COVID-19. In doing so, we found a total of 13 shared genes, which may be the link between ferroptosis and COVID-19. Our research may provide new clues and ideas for future research on ferroptosis and COVID-19.

3.1. Research trends

To obtain the relevant publications on ferroptosis from 2012 to 2023, we extracted 11,140 publications from the database. Between 2012 and 2023, publications regarding ferroptosis have increased each year and started to increase rapidly since 2018 (Fig. 1). Less than 100 articles were published before 2016 and more than 100 publications appeared each year from 2017. These results illustrated the gradual and widespread interest in the study of ferroptosis.

3.2. Journals and co-cited journals

To obtain journals on ferroptosis from 2012 to 2023, we isolated 200 journals relevant to ferroptosis. As shown in Table 1, of the first ten journals, half of the journal articles exceed 200, with a difference of one paper between the first and second. The Journals, Free Radical Biology & Medicine, Frontiers in Oncology, and Cell Death & Disease, published 236, 235, and 214 articles respectively.

We counted 374 co-cited journals, with 87 journals having more than 1,000 citations and 4 journals having more than 5000 citations. As shown in Table 2, Cell had the highest number of co-citations with 7935, followed by Nature and Proceedings of the National Academy of Sciences of the United States of America with 6088 and 5176 citations, respectively. Cell was recognized as the

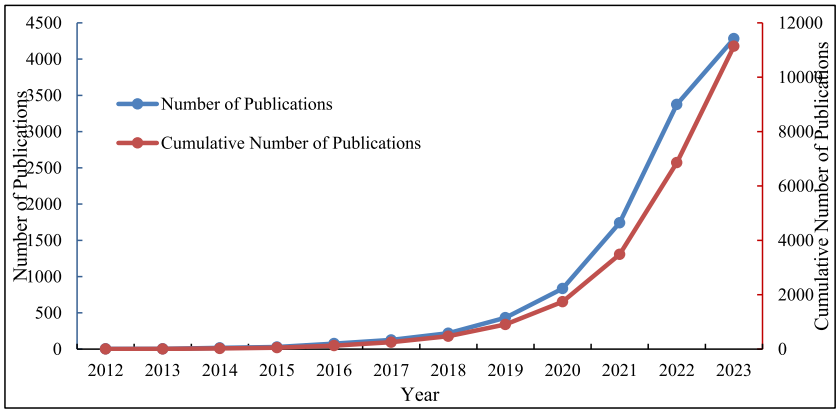

Fig. 1. From 2012 to 2023, the number of publications regarding ferroptosis each year has been steadily increasing.

leading journal in ferroptosis research and was cited far more highly than other journals. The number of Co-Cited journals included in the study was 87 journals with 192324 occurrences (Fig. 2). These results illustrated the close collaboration between different journals and the contribution of each journal to ferroptosis research. As can be seen in Fig. 2, Cell was co-directed to the journal Free Radical Biology and Medicine, which means that current research related to ferroptosis is focused on basic research, gradually transforming medical research.

3.3. Contribution of countries and institutions

In quantifying research on ferroptosis by country and institution from 2012 to 2023, we found 101 countries and 349 institutions with research relating to ferroptosis. As shown in Table 3, the highest number of articles was from China with 7578 articles, accounting for 68.03 % of all publications, followed by the United States, Germany, Japan, and Italy with 1698, 455, 411, and 237 articles respectively. The United States and China were both centers of ferroptosis research and hold very important roles in the progress of ferroptosis research (Fig. 3A).

A total of 349 institutions have issued publications about ferroptosis of which 9 of the top 10 scientific institutions were from China (Table 4). Most of the research organizations were from China (Fig. 3B). There was close cooperation among different institutions. The institution with the most published papers was Central South University with 361 papers, followed by the Chinese Academy of Sciences and Shanghai Jiao Tong University. A total of 7 research institutions had high egocentricity greater than 0.10. The largest egocentricity was the Chinese Academy of Sciences with 0.2, followed by the University of Washington Seattle and Columbia University, with 0.15 and 0.13, respectively. These results indicated that more and more countries and institutions are starting to make a great contribution to ferroptosis research with varying degrees of close cooperation.

3.4. Authors analysis

To obtain data on the authors and co-cited authors of ferroptosis studies from 2012 to 2023, we downloaded the relevant information from the database. The authors were included in a study and their number of publications was counted, from which a collaborative knowledge map was generated (Fig. 4). A total of 34 authors were included in the co-occurrence chart, appearing 1546 times.

Authors who were co-cited in other literature were co-cited authors [45]. We counted 1149 co-cited authors, 24 of whom were co-cited more than 1000 times. The co-cited authors included in the study were counted to generate a 248-node co-citation knowledge graph (Fig. 5).

As shown in Table 5, the most published article was Tang DL with 109 articles, followed by Kang R, Conrad M, and Stockwell BR, with 99, 79, and 75 articles, respectively. The top 10 authors contributed a total of 652 articles on ferroptosis research, and 113 authors published more than 10 articles. The node linkage formed several teams, such as Stockwell BR, Conrad M, Tang DL, etc. The number of research teams was high and there was close cooperation within the teams, indicating active collaboration among the authors.

As shown in Table 5, the highest number of co-citations was Dixon SJ with 6060, followed by Yang WS, Stockwell BR, Doll S, and Angeli JPF, with 3984, 3535, 2306, and 2299, respectively. The top 10 authors, with a total number of co-citations of 27007, accounted for 13.89 % of the total authors. These results indicate a high number of ferroptosis-related research teams and cooperation among different teams.

3.5. Knowledge base analysis

To analyze the co-cited references on ferroptosis research from 2012 to 2023, we obtained the relevant data from the database and the top ten co-cited references are listed in Table 6.

We found that the top 10 co-cited references focused on studying the basis of ferroptosis, including mechanisms of ferroptosis and ferroptosis-related diseases. In 2012, the first article on ferroptosis was published in Cell by Dixon SJ et al. [39]. The article summarised the concept of ferroptosis and showed that this novel form of cell death was distinct from other forms of cell death at the morphological, generation mechanism, and biochemical levels. In 2017, an article on ferroptosis was published in Cell by Stockwell BR

Table 1
Top 10 journal publications.

Rank	Journal	Counts (%)	IF (2024)
1	Free Radical Biology and Medicine	236 (2.12)	7.4
2	Frontiers in oncology	235 (2.11)	4.7
3	Cell Death & Disease	214 (1.92)	9.0
4	International Journal of Molecular Sciences	211 (1.89)	5.6
5	Frontiers in pharmacology	209 (1.88)	5.6
6	Frontiers in cell and developmental biology	193 (1.73)	5.5
7	Redox biology	149 (1.34)	11.4
8	Antioxidants	135 (1.21)	7.0
9	Frontiers in genetics	133 (1.19)	3.7
10	Frontiers in Immunology	128 (1.15)	7.3

Table 2
Top 10 cited journal.

Rank	Journal	Counts (%)	IF (2024)
1	Cell	7935 (2.52)	64.5
2	Nature	6088 (1.94)	64.8
3	PNAS	5176 (1.65)	11.1
4	Free Radical Biology and Medicine	5072 (1.61)	7.4
5	Cell Death & Disease	4992 (1.59)	9.0
6	Cell death & differentiation	4749 (1.51)	12.4
7	Nature Communications	4437 (1.41)	16.6
8	Journal of Biological Chemistry	4037 (1.28)	4.8
9	Redox Biology	3921 (1.25)	11.4
10	International Journal of Molecular Sciences	3829 (1.22)	5.6

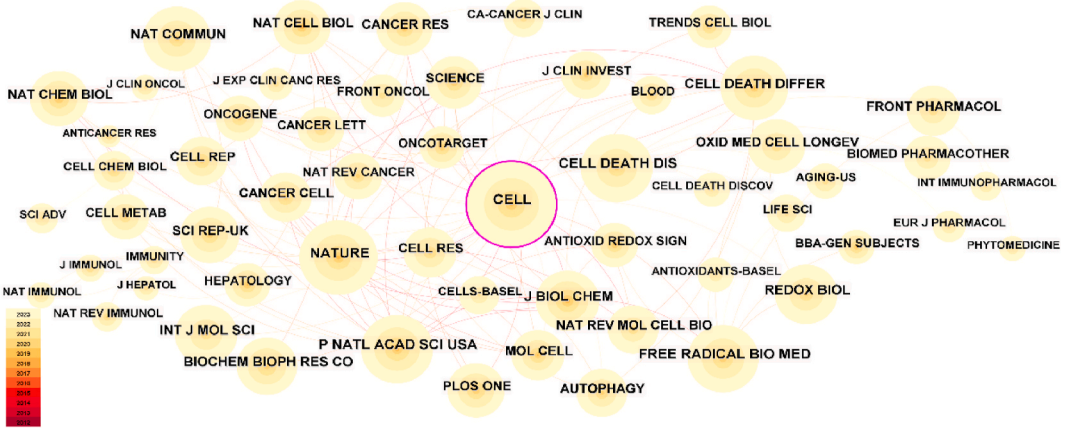

Fig. 2. Journal co-citation co-occurrence graph (T ≥ 1000).

Table 3
Top 10 countries/regions issued papers.

Rank	Country	Counts (%)	Year
1	China	7578 (68.03)	2014
2	USA	1698 (15.24)	2012
3	Germany	455 (4.08)	2013
4	Japan	411 (3.69)	2014
5	Italy	237 (2.13)	2015
6	France	184 (1.65)	2013
7	South Korea	184 (1.65)	2015
8	Australia	183 (1.64)	2016
9	Canada	155 (1.39)	2015
10	England	148 (1.33)	2014

et al. [46] and the most co-cited article (n = 1999). This literature summarised the underlying mechanisms of ferroptosis, highlighting the links with other areas of biology and medicine. In 2021, the second co-cited experimental research by Jiang XJ and others [47] was published by Nature Reviews Molecular Cell Biology. This literature provided an overview of the mechanisms of ferroptosis and discussed the effects of ferroptosis on disease. The third co-cited experimental research by Bersuker K [48]and others was published by Nature in 2019. This article identified a ferroptosis inhibitory pathway and indicated that pharmacological inhibition of FSP1 may provide an effective strategy to sensitize cancer cells to ferroptosis-inducing chemotherapeutic agents, which was important for the treatment of cancer.

3.6. Analysis of COVID-19

To obtain the relationship between COVID-19 and ferroptosis, a total of 304 ferroptosis-related genes and 2572 COVID-19-related genes were mined from the Genecards database. Based on the condition of relevance score >1 and protein coding-related genes, 127 ferroptosis-related genes, and 553 COVID-19-related genes were finally screened. Finally, 13 common genes were isolated after the intersection using Wayne (Fig. 6A). The shared genes were Nuclear factor erythroid 2-related factor 2 gene (Nrf2), Heme oxygenase 1

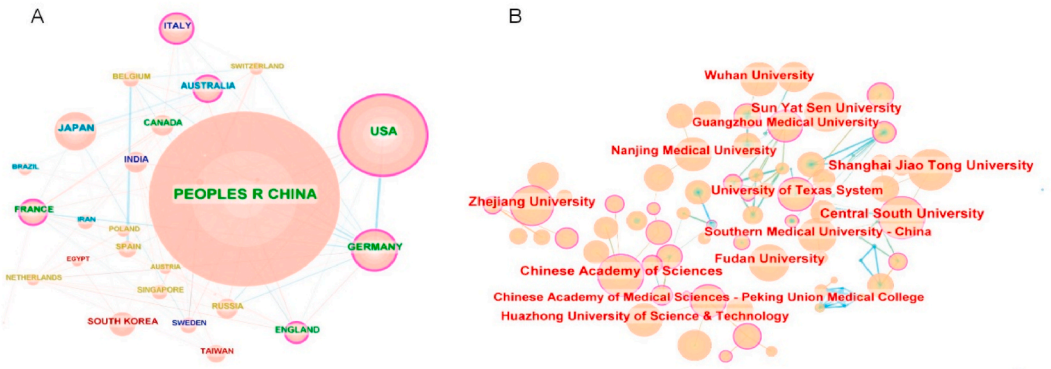

Fig. 3. Co-occurrence plots for (A) countries (T ≥ 30) and (B) institutions (T ≥ 100). Notes: The node size indicates the number of publications, and the connecting line indicates the collaboration relationship. Different colors indicate different years. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Top 10 institutions issued papers.

Rank	Institute	Counts (%)	Year
1	Central South University (China)	361 (3.24)	2014
2	Chinese Academy of Sciences (China)	350 (3.14)	2015
3	Shanghai Jiao Tong University (China)	350 (3.14)	2018
4	Sun Yat Sen University (China)	323 (2.90)	2018
5	Zhejiang University (China)	311 (2.79)	2018
6	Fudan University (China)	282 (2.53)	2019
7	Southern Medical University (China)	250 (2.24)	2019
8	University of Texas System (USA)	245 (2.20)	2014
9	Nanjing Medical University (China)	240 (2.15)	2020
10	Wuhan University (China)	240 (2.15)	2019

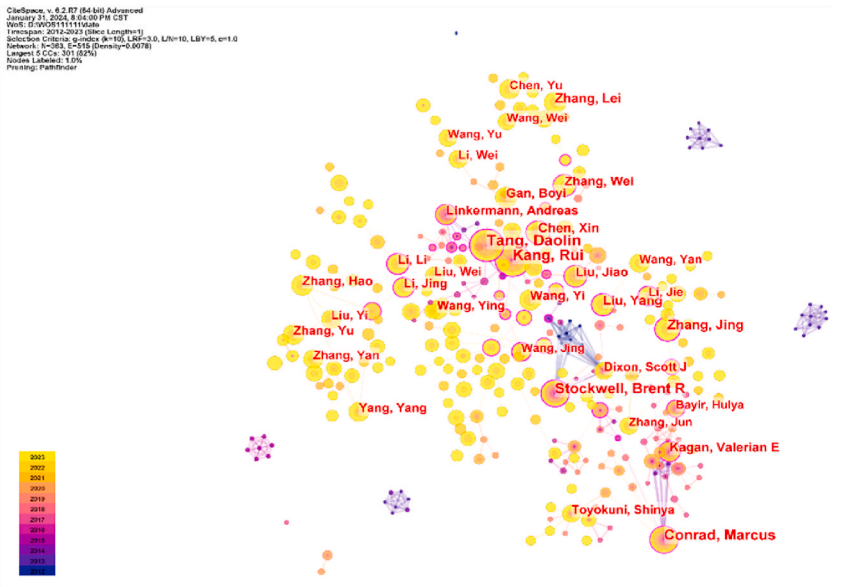

Fig. 4. Co-occurrence plots for author collaboration (T ≥ 30). Notes: The node size indicates the number of publications and the connecting line indicates the collaboration relationship. Different colors indicate different years. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

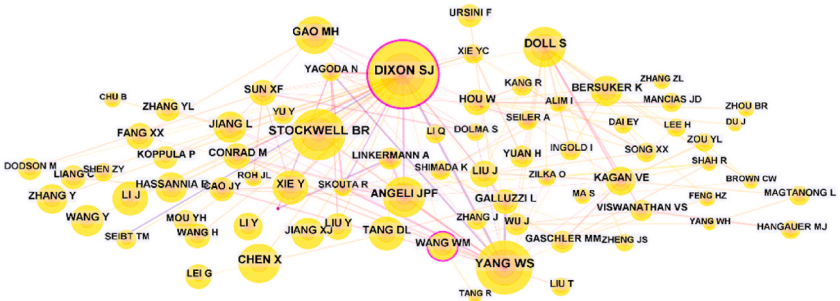

Fig. 5. Co-occurrence plots for author co-citation analysis (T $\geq$ 200). Notes: The node size indicates the number of publications and the connecting line indicates the collaboration relationship. Different colors indicate different years. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 5
Top 10 authors issued papers and top 10 cited authors.

Rank	Author	Counts (%)	Co-cited author	Citations (%)
1	Tang, Daolin	109 (2.60)	Dixon SJ	6060 (3.12)
2	Kang, Rui	99 (2.36)	Yang WS	3984 (2.05)
3	Conrad, Marcus	79 (1.88)	Stockwell BR	3535 (1.81)
4	Stockwell, Brent R	75 (1.79)	Doll S	2306 (1.19)
5	Zhang, Jing	52 (1.24)	Angeli JPF	2299 (1.18)
6	Chen, Xin	51 (1.22)	Chen X	2134 (1.10)
7	Zhang, Lei	48 (1.14)	Gao MH	1992 (1.02)
8	Liu, Yang	47 (1.12)	Xie Y	1670 (0.86)
9	Zhang, Wei	46 (1.10)	Li J	1530 (0.79)
10	Gan, Boyi	46 (1.10)	Tang DL	1497 (0.77)

Table 6
Top 10 total literature citations.

Rank	Cited Reference	Year	Co-citation
1	STOCKWELL BR, 2017, CELL, V171, P273, DOI 10.1016/J.CELL.2017.09.021	2017	1999
2	Jiang XJ, 2021, NAT REV MOL CELL BIO, V22, P266, DOI 10.1038/s41580-020-00324-8	2021	1276
3	Bersuker K, 2019, NATURE, V575, P688, DOI 10.1038/s41586-019-1705-2	2019	1234
4	Doll S, 2019, NATURE, V575, P693, DOI 10.1038/s41586-019-1707-0	2019	1183
5	Li J, 2020, CELL DEATH DIS, V11, P0, DOI 10.1038/s41419-020-2298-2	2020	1101
6	Hassannia B, 2019, CANCER CELL, V35, P830, DOI 10.1016/j.ccell.2019.04.002	2019	1038
7	Doll S, 2017, NAT CHEM BIOL, V13, P91, DOI 10.1038/NCHEMBIO.2239	2017	1020
8	Wang WM, 2019, NATURE, V569, P270, DOI 10.1038/s41586-019-1170-y	2019	990
9	Tang DL, 2021, CELL RES, V31, P107, DOI 10.1038/s41422-020-00441-1	2021	896
10	Chen X, 2021, NAT REV CLIN ONCOL, V18, P280, DOI 10.1038/s41571-020-00462-0	2021	804

(HMOX1), Beclin 1 (BECN1), Activating transcription factor 4 (ATF4), RELA proto-oncogene (RELA), Highmobility group box protein 1 (HMGB1), Jun proto-oncogene (JUN), Cytochrome *b*-245 beta chain (CYBB), Ferritin light chain (FTL), Chemokine (C-C motif) ligand 5 (CCL5), Tumour necrosis factor (TNF), Mitogen-activated protein kinase 1 (MAPK1), and Suppressor of cytokine signaling-1 (SOCS1). The 13 shared genes were enriched and were Gene Ontology (GO) analyzed by R language (version 4.04, cluster profile, org. Hs.eg.db, enrichplot and ggplot2) (Fig. 6).

As shown in Fig. 6B, the number of genes enriched in Lipid and atherosclerosis was the highest, with 7 genes including the Tumour necrosis factor (TNF) signaling pathway, NOD-like receptor signaling pathway, Shigellosis, Alzheimer's disease, and Pathways of neurodegeneration-multiple disease including the same number of genes. The TNF signaling pathway was not as abundant as Lipid and atherosclerosis, but the enrichment was higher. These results suggested that the TNF pathway may be a novel pathway for the treatment of COVID-19.

As shown in Fig. 6C, the number of genes accumulated in the cellular response to oxidative stress, cellular response to chemical stress, response to oxidative stress, and response to nutrient levels, were the largest. While the number of genes accumulated in phosphatidylinositol 3-kinase complex, transcription repressor complex, caveola, chemoattractant activity, repressing transcription factor binding, activating transcription factor binding, phosphoric diester hydrolase activity, phospholipase activity, and lipase activity, were smallest. The cellular response to oxidative stress had the highest enrichment, suggesting that the oxidative stress response in iron-dead cells may have a relationship with COVID-19.

As detailed in Fig. 6D and E, TNF, RELA, MAPK1, and HMOX1 were associated with response to nicotine. TNF, RELA, ATF4, CYBB,

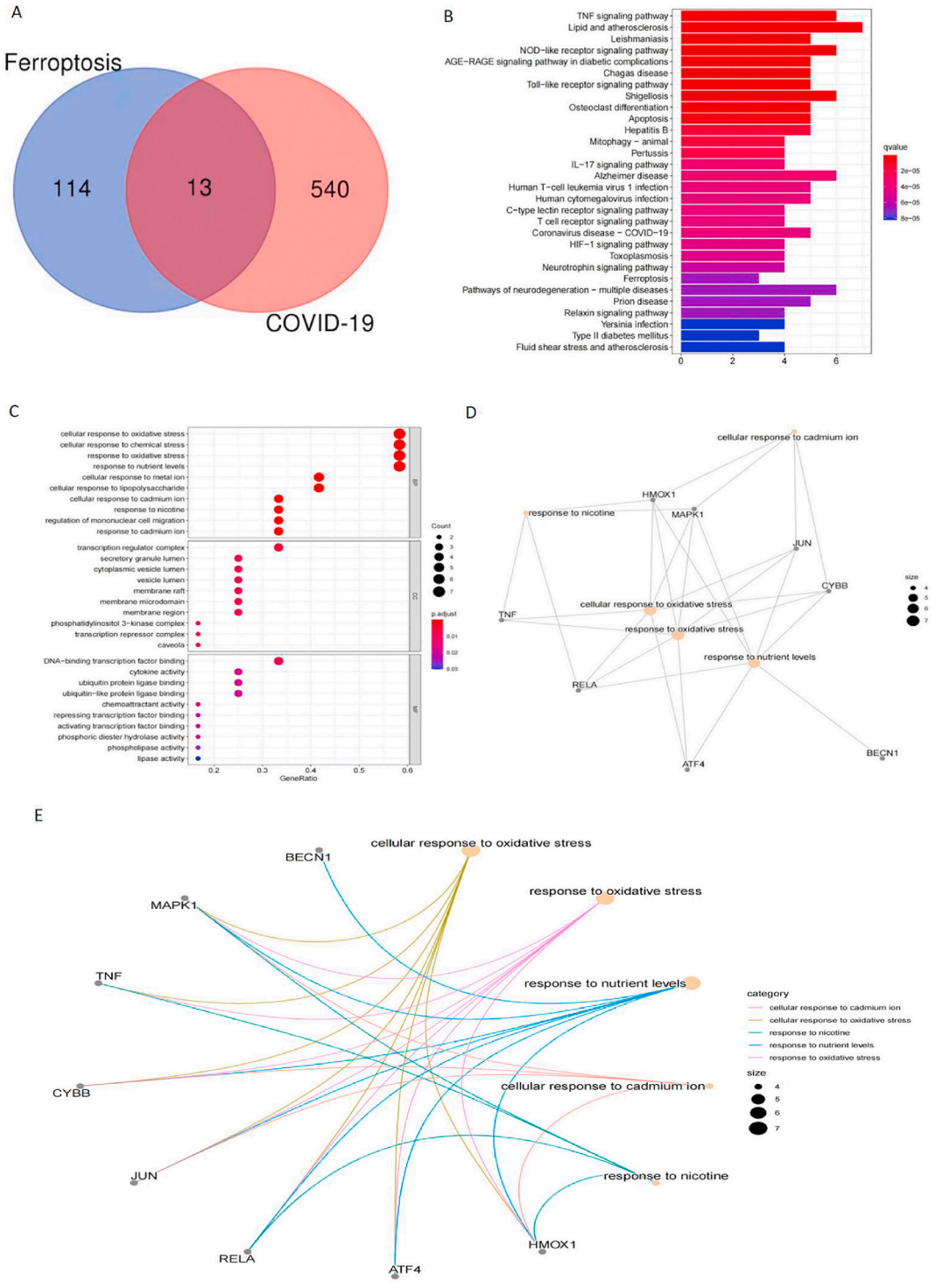

Fig. 6. (A) Ferroptosis-related genes and COVID-19-related genes were intersected by a Venn diagram. (B) The number of genes enriched in different Pathways. (C) The ratio of genes in the enriched to term. (D) Graph of the relationship between shared genes and different responses. (E) Graph of the relationship between shared genes and different responses. Notes: Different colors represent different levels of enrichment, the redder the color, the higher the level of enrichment, and the size of the dot indicates the number of genes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

JUN, MAPK1, and HMOX1 have an association with cellular response to oxidative stress. RELA, ATF4, BECN1, CYBB, JUN, MAPK1, and HMOX1 were associated with response to nutrient levels. TNF, RELA, CYBB, JUN, MAPK1, and HMOX1 were associated with response to oxidative stress. While HMOX1, MAPK1, JUN, and CYBB, were associated with cellular response to cadmium ion. These results suggested that the seven genes (TNF, RELA, ATF4, CYBB, JUN, MAPK1, and HMOX1) are associated with oxidative stress and that these seven genes may be the breakthrough between ferroptosis and COVID-19.

Taken together, the above results suggest that there is a relationship between COVID-19 and ferroptosis and that the TNF pathway may be a novel pathway for the treatment of COVID-19. Seven genes, including TNF, RELA, ATF4, CYBB, JUN, MAPK1, and HMOX1, were also linked to oxidative stress. Therefore, these seven genes may be a breakthrough in linking ferroptosis and COVID-19.

4. Discussion

4.1. General information

The COVID-19 pandemic has been the focus of the world in recent years. Similarly, ferroptosis has developed rapidly in recent years and has been the focus of several scientists and organizations. Ferroptosis is the most recently discovered mode of regulated cell death. Since the discovery of ferroptosis, it has been demonstrated to play a very important role in some diseases [49–52]. In today's world, the COVID-19 epidemic is not over, and the emergence of SARS-CoV-2 Omicron variants has triggered a fourth wave of the pandemic in many countries around the world [53]. COVID-19 not only affects our lives but also deeply affects the world's economy. Thus, only by finding a solution to COVID-19 as soon as possible, can our lives return to normal. As a rapidly developing field of research, ferroptosis-related publications are growing in number (Fig. 1). So, is there any connection between ferroptosis and COVID-19? Studies have reported that SARS-CoV-2 significantly suppressed the mRNA expression of GPX4, which is associated with ferroptosis [31]. We speculate that ferroptosis may provide a way to study COVID-19. To better understand the relationship between ferroptosis and COVID-19, we conducted this study. Previously, several articles performed bibliometric analyses of ferroptosis [54–56]. However, there had been no visual analysis of ferroptosis in COVID-19, and to the best of our knowledge, this is the first study to visualize ferroptosis and COVID-19.

The annual publication volume represents the trend of the research field [57], We have found that since the emergence of ferroptosis, research has gradually gained attention and maintained a certain research fervour. The number of ferroptosis-related articles published in 2012 was just 3 and only 3 in 2013. From 2014 to 2016 the number of articles issued showed stable growth and entered double digits. The number of articles issued increased rapidly since 2017, reaching triple digits every year thereafter, with each successive year seeing approximately twice the number of articles of the previous - which is a rapid growth stage [55]. Wu Haiyan et al. indicate a stepwise increase in global ferroptosis research publications until 2017, whereas the recent 3 years have displayed a significant level of increase [55]. We agree that the research on ferroptosis is getting more and more attention, which indicates that a clear growth trend will likely be maintained in the future.

The number of articles published in a country represents the level of research in the field. We counted 11140 articles on ferroptosis from 101 countries and found that China is still the country with the highest number of articles, accounting for about 68 %. Of the top 10 countries, only China is a developing country, indicating that the ferroptosis problem is predominantly receiving attention from developed countries. A reason for this might be that developed countries have sufficient funding for solid science and technology to support ferroptosis research [58], which is consistent with findings by Zhang Jie et al. [54]. The results show that China is a major country in the study of ferroptosis. Although China is not the first country to study ferroptosis, it is the country with the most published articles in this area. Whereby, China's efforts have achieved good results and made outstanding contributions to the study of ferroptosis. These results show that studies regarding ferroptosis have gained a lot of attention worldwide.

Do different institutions differ in their ferroptosis research? Our study found that the top 30 research institutions were primarily from China and the United States. This was probably because the largest number of ferroptosis research-related publications were contributed by China, followed by the United States. Central South University was the institution with the most publications from China. The University of Texas System was the institution with the most publications from the United States. Zhang Jie et al. believe that China and the United States have made outstanding contributions to the study of ferroptosis [54]. At the same time, these results suggest that the scientific and technological strength of a country cannot be separated from the support of scientific research institutions. We also found that there was close cooperation between a number of different institutions, including domestic organization cooperation and international organization cooperation, which again indicates potential growth trends for the future. Whilst each institution may have its own research direction, this could strengthen cooperation and opportunities to carry out high-level exchanges of information [59].

Among 11140 articles on ferroptosis, we found that Cell is still the journal with the highest number of co-cited references and is cited more frequently than other journals. The number of publications on ferroptosis in journals reflects the journal's status in ferroptosis research to a certain extent [57]. Until now, the current ferroptosis-related research has been focused on the study of disease. More and more journals are reporting ferroptosis studies, suggesting that a certain growth trend will be maintained in the future.

The development of ferroptosis cannot be achieved without the contribution of each researcher, where ferroptosis knowledge has developed so rapidly due to the joint efforts of these researchers. We found that Stockwell BR, Conrad M, Kagan VE, Chen X, Zhang Y, Dixon SJ, and Tang DL, are not only in the top 20 authors' co-citation ranking but also in the top 20 authors' collaboration ranking, indicating that these seven authors have made outstanding contributions to the field of ferroptosis. We also found active collaboration between different institutions with good results. For example, in 2012 twelve researchers from different institutions jointly published one of the most influential articles on the topic [39]. Each author had their own research direction, and it is this kind of mutual

collaboration among authors that should be encouraged to accelerate the pace and depth of ferroptosis research, to explore and discover more secrets about ferroptosis.

4.2. Hot topic analysis: COVID-19

After the SARS-CoV-2 invaded the human, it mainly attacked cells that expressed a large amount of ACE2. The main cell types were: type II alveolar epithelial cells, nasal ciliary cells, goblet cells, nodes, some cells in the ileum, and cells expressing ACE2 protein in smooth muscle tissue. Up to now, the downregulation of ACE2 is widely believed to be closely related to severe lung injury and multiple organ injury [60]. Diseases such as tumors, neurological diseases, infectious diseases, and COVID-19 pneumonia, are all related to inflammation [61–63]. A co-cited article with high centrality describes mechanisms in inflammation [64]. Also, one study identified the role of ferroptosis in inflammatory diseases [65]. These findings have contributed significantly to subsequent studies. Inflammation is one of the biological features of malignant tumors [66]. To address the problem of inflammation in tumors, Liu et al. [67] found that, OTU domain-containing ubiquitin aldehyde-binding proteins 1 (OTUB1) mediated with solute carrier 7A11 (SLC7A11), stably inhibited the ferroptosis response in tumors to achieve tumour non-expansion. However, this approach has some limitations, as the inhibitory effect is reversed once SLC7A11 is overexpressed. Ferroptosis also plays an important role in cardiovascular diseases. Wang Fulong et al. [68] found that the downregulation of SLC7A11 led to the deficiency of intracellular cystine and reduced GSH, which were the main mechanisms that induced ferroptosis in cardiomyocytes. We have learned that SLC7A11 can block ferroptosis in cardiomyocytes and thus effectively reverse the cardiomyopathy caused by transferrin deficiency, which is of great importance for the treatment of heart diseases. Pathogenic infections are often accompanied by an inflammatory response [69]. Dar et al. [70] found that lipoxygenase (LOX) secreted by bacteria-induced phospholipid oxidation in lung epithelial cells, led to ferroptosis in the host cells. This finding has provided a new way of thinking about the therapy of respiratory diseases associated with *P. aeruginosa* infection. There are few studies on ferroptosis in infectious diseases, and the mechanism of ferroptosis is not well understood. However, the above findings suggest that ferroptosis may be involved in the development of infectious diseases of certain pathogens.

As a new type of cell death, ferroptosis has many secrets to be discovered, especially for some major diseases. Since 2019, the COVID-19 outbreak has occurred worldwide and has caused more than 7 million people to lose their lives. Therefore, it is urgent to address COVID-19. We identified 13 shared genes (Nrf2, HMOX1, BECN1, ATF4, RELA, HMGB1, JUN, CYBB, FTL, CCL5, TNF, MAPK1, SOCS1) from the Genecards database, mined for ferroptosis and COVID-19-related genes. We think that these 13 shared genes may be new targets for the future treatment of COVID-19. We found 6 shared genes in the TNF pathway and the highest gene enrichment. Rajendra Karki et al. found that mortality-related acute lung injury and excessive production of proinflammatory cytokines are the main characteristics of COVID-19. It was also found that neutralizing antibodies against TNF-α and IFN-γ could protect mice from death when they were infected with severe COVID-19 and during sepsis [71].

Studies have reported that the abnormal expression of TNF family cytokines is related to human diseases and can act as extracellular cytokines to activate various signaling pathways of inflammation and apoptosis [72]. In addition, Zhang's group found that TNF-α inhibited the effects of leptin on β cell survival and apoptosis, as well as insulin secretion and synthesis [73], while iron or Fenton reaction shows the same significant role in pancreatic β cells [74,75]. To be more specific, Fe^{2+} oxidizes lipids through the Fenton reaction, promoting the production of large amounts of ROS, which then mediates the continuous oxidation of DNA and proteins, leading to reduced insulin synthesis and secretion, and ultimately to apoptosis [76]. We believe that the TNF pathway may be a new target for the treatment of COVID-19, but unfortunately, we have only undertaken informatics analysis, so further studies are still needed. MAPK, mitogen-activated protein kinase, can not only inhibit cell proliferation but also mediate cell apoptosis. Some studies have revealed that the lower levels of MAPK1 protein were observed in COVID-19-infected patients, and the severity of the disease increases, indicating that MAPK1 may inhibit the proliferation of COVID-19 to relieve the condition [77]. Additionally, researchers have reported that patients with COVID-19 pneumonia have severe inflammation [78,79]. Amara [80] et al. found that the main feature of COVID-19 is the production of an inflammatory cytokine associated with oxidative stress, which can cause lung damage and respiratory distress. Our study found that the proportion of shared genes in the oxidative stress response of cells is large, and that enrichment is high. Seven genes, including TNF, RELA, ATF4, CYBB, JUN, MAPK1, and HMOX1, are linked to oxidative stress. To sum up, the seven genes may be the breakthrough in linking ferroptosis and COVID-19, but their specific relationship is not yet clear and needs to be further investigated. Furthermore, these results suggest that oxidative stress is a key factor in severe COVID-19 and that ferroptosis may play a role in this disease. Wang, Y. J et al. infected African green monkey kidney cells with patient-derived SARS-CoV-2 and found that the mRNA level expression of GPX4 was significantly reduced in African green monkey kidney cells, suggesting a possible association between SARS-CoV-2 and ferroptosis [31]. The present results suggest that SARS-CoV-2 may induce ferroptosis by inhibiting GPX4, but the related mechanism is not fully understood and needs to be further investigated. A clinical study found that COVID-19 patients showed systemic signs of ferroptosis during the first days of intensive care unit (ICU) admission and that these markers had different outcomes in the ICU [81]. We could "personalized" treatment allocation to critically ill COVID-19 patients based on systemic biomarker profiles.

Since the outbreak of COVID-19, scientists around the world have been working on a vaccine [82–85]. Researchers recently injected a small number of COVID-19 patients with N-acetylcysteine and the study found that the patient's symptoms improved [86]. This suggests that N-acetylcysteine might be useful for the therapy of patients with COVID-19, but few clinical trials have been performed. Whether intravenous N-acetylcysteine has a significant effect in humans will therefore need to be confirmed by additional clinical trials. Codo et al. [87] found that N-acetylcysteine inhibited the stability of hypoxia-inducible factor-1α (HIF-1α) and blocked the expression of SARS-CoV-2, which in turn inhibited the replication of SARS-CoV-2. Therefore, we suggest that N-acetylcysteine may have a positive effect on the treatment of COVID-19. Liu et al. found that Saquinavir, Hypericin, Baicalein, and Bromocriptine, could

bind to the N-terminus and C-terminus of the SARS-CoV-2 non-structural protein 14 (NSP14) homology model, and these drugs all interacted with key amino acid residues in the active center, by modeling analysis and virtual screening [88]. Furthermore, Liang et al. unveiled that Baicalein increased the expression of ferroptosis-related proteins such as SLC7A11, GPX4, and FTH to inhibit ferroptosis both in vitro and in vivo [89]. Although the mechanism of the reaction between the relevant natural products and ferroptosis is not clear, we believe that these four compounds are important in further studies related to the interaction between SARS-CoV-2 and ferroptosis.

The above studies suggest that inflammatory diseases, and more recently COVID-19 pneumonia, have a very important relationship with ferroptosis. In the future, an in-depth study of the relationship between ferroptosis, inflammatory diseases, and COVID-19 pneumonia, could provide a more comprehensive understanding of the occurrence and development of the diseases, providing new ideas for their treatment.

This study also has some limitations. First, we searched and gathered information from the WoSCC database only and may have missed other data related to ferroptosis. Second, all data for this study was retrieved and collected before December 30, 2023, thus new updates would be missed.

5. Conclusion

Research related to ferroptosis is still in a rapidly developing stage. China and the United States have emerged with strong scientific creativity. More cooperation is needed between countries, institutions, and authors. By analyzing shared genes between ferroptosis and COVID-19, we saw that most of the shared genes are enriched in the TNF pathway and that the largest number of genes are up-regulated under the cellular response to oxidative stress - which may serve to be the focus of future research on ferroptosis and COVID-19. We believe that the results of this study can provide useful references for future research.

Funding

This work was supported by the National Natural Science Foundation of China (NO.31870135), the Funded by CMC Excellent-talent Program (2024kjTzn01), and the Research Fund of Chengdu Medical College (CYZZD23-04).

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because it donot include any human or animal participation.

Data availability statement

All data accessed and analyzed in this study are available in the article and its supplementary materials.

CRediT authorship contribution statement

Junda Zhou: Writing – review & editing, Writing – original draft, Visualization. **Wenjia Ni:** Writing – review & editing, Formal analysis, Data curation. **Xianqin Zhang:** Data curation. **Meng Yang:** Software, Resources. **Xin Liu:** Supervision. **Jinlin Guo:** Methodology, Investigation. **Jian Li:** Validation. **Qi Zhao:** Formal analysis. **Hang Deng:** Resources, Project administration, Methodology. **Hanyue Lei:** Visualization, Methodology, Investigation. **Lin Zhang:** Writing – review & editing, Visualization, Data curation. **Hai Liao:** Writing – review & editing, Writing – original draft, Visualization. **Xu Jia:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank all the participants who participated in this study.

Abbreviation

COVID-19	coronavirus disease 2019
LPO	lipid peroxidation
ROS	reactive oxygen species
GSH	Glutathione
GPX4	glutathione peroxidase 4
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

GDP	Gross Domestic Product
WoSCC	Web of Science Core Collection
Nrf2	Nuclear factor erythroid 2-related factor 2 gene
HMOX1	Heme oxygenase 1
BECN1	Beclin 1
ATF4	Activating transcription factor 4
RELA	RELA proto-oncogene
HMGB1	Highmobility group box protein 1
JUN	Jun proto-oncogene
CYBB	Cytochrome *b*-245 beta chain
TNF	tumor necrosis factor
FTL	Ferritin light chain
CCL5	Chemokine (C-C motif) ligand 5
MAPK1	Mitogen-activated protein kinase 1
SOCS1	Suppressor of cytokine signaling-1
OTUB1	OTU domain-containing ubiquitin aldehyde-binding proteins 1
SLC7A11	solute carrier 7A11
LOX	lipoxygenase
HIF-1α	hypoxia-inducible factor-1α
NSP14	non-structural protein 14
GO	Gene Ontology
ICU	intensive care unit

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37617.

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