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Original Article

A comprehensive and visualized analysis of relationship between ferroptosis and tumor using bibliometrics and bioinformatics

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Abstract: This study aimed to summarize the current developments and hub genes in the ferroptosis field using bibliometrics and bioinformatics and provide guidance for future developments. The publications on ferroptosis from 2012 to 2021 were extracted from the Web of Science database. VOSviewer software and CiteSpace software were used to visualize and predict the trend of ferroptosis research. The key genes related to ferroptosis were selected from the Web of Genecards, and Kyoto Encyclopedia of Genes and Genomes (KEGG)/Gene Ontology (GO) analysis was performed. Cytoscape software and online survival curve analysis platform were also used to screen hub genes and analyze their roles. Chinese researchers published the highest number of publications in this field, while American publications exhibited higher quality. In terms of institutions, Central South University and Zhejiang University have the highest number of publications. *Cell Death Disease* published more studies than other journals. The application of ferroptosis is a major research area, and, importantly, "RCD", "FTH1", and "nomogram" are the keywords. We also found tumor-related pathways of interest in the field of ferroptosis. *Sirtuin 3 (SIRT3), Glutathione Peroxidase 4 (GPX4), and transferrin receptor (TFRC)* genes were of significance for the prognosis of tumors. The number of publications on ferroptosis may increase in the future. Cooperation among countries and disciplines is particularly important in this regard. Also, the applications of ferroptosis, especially in chemotherapy and immunotherapy for tumors, will be the focus of future research. Keywords "RCD", "FTH1", and "nomogram" is receiving high attention, and in-depth studies on tumor-related genes *SIRT3*, *GPX4*, and *TFRC* may provide new therapeutic targets.

Keywords: Cancer, chemotherapy, ferroptosis, GPX4, immunotherapy, pan-cancer analysis, SIRT3, TFRC

Introduction

Ferroptosis is a new type of programmed cell death different from apoptosis, necrosis, and autophagy. It is closely related to the level of reactive oxygen species (ROS) in body. The research of ferroptosis has seen exponential growth over the past few years, since the term was coined in 2012 [1]. It has been applied to the biomedical field, including cell metabolism and senescence [2], immune process [3], and tumor therapy [4]. In cellular metabolism and senescence, the most striking feature of iron intoxication is that the process is induced by the accumulation of unrepaired cellular damage rather than being mediated by an active mechanism [5]. Compared with apoptosis, autophagy, and pyroptosis, the effect of ferroptosis on cell biological processes is even more significant [6]. The unique pattern of cell death, which driven by iron-dependent phospholipid peroxidation, is associated with multiple cellular metabolic pathways, including redox homeostasis, iron processing, mitochondrial activity, also including metabolism of amino acids, sugars, and lipids [7]. All of these have an impact

on biological processes, thus influencing cellular metabolism and senescence. Similarly, ferroptosis also plays an important role in immunity and immune clearance process. It can also reduce the number of T and B cells in the immune response against pathogens [8]. Meanwhile, phagocytes can eliminate ferroptotic cells by mediating membrane receptors such as toll-like receptor 2 (TLR2), making immunization more thorough and safe [9]. In terms of mechanism, the upstream inducers of ferroptosis can be divided into two categories, biological factors and chemical factors, and activate two main pathways, exogenous and enzymatic pathways [10], which is strongly associated with the regulation of the immune response. Therefore, elucidating the intersection between cell death and immunity through this process would be a major advance in new treatments for immune diseases [10]. Cancer cells have an increased demand for iron compared to normal non-cancer cells. Iron dependence can make cancer cells more susceptible to iron-catalyzed necrosis [11]. Therefore, its effect on tumors should not be underestimated. The interaction of iron deposition with other bioactive substances can regulate various processes in tumor occurrence, tumor immunity and tumor drug resistance, especially various enzymes related to ROS, which have received attention in recent years [12]. Studies have shown that ferroptosis has great potential for antitumor resistance and is considered a viable therapeutic strategy for eliminating residual or resistant cancer cells [13]. At present, a large number of studies on the relationship between ferroptosis and cancer provide a prospect for the treatment of cancer, as well as drug-resistant tumors. As a result, researchers and institutions are expanding their exploration of the sites associated with ferroptosis.

Bibliometrics is a scientific method that uses qualitative and quantitative methods to evaluate articles. The contributions of the academic community and individual researchers are evaluated by summarizing the basic information of the included research literature. At the same time, by taking the core keywords of the research as the focus, in-depth analysis is carried out to provide evidence for future development trend [14]. Bioinformatics analysis is a computer-based method that addresses biological problems by comprehensively utilizing biology, computer science, and information technology to analyze a large amount of complex biological data. Life science and computer science are combined through the collection, processing, and analysis of biological information to predict the research direction and obtain clinically instructive results [3].

Currently, there are no comprehensive bioinformatics and bibliometrics analyses simultaneously focusing on the important process of ferroptosis. Therefore, such studies need to be urgently conducted. In order to fill this gap, the present study analyzed the applied research progress of ferroptosis based on the articles published on the Web of Science (WOS) and the related genes from the website (*https://www.genecards.org*), using bibliometrics and bioinformatics analysis methods.

Materials and methods

Bibliometric

Data sources and search strategies of bibliometric: We adopted common research methods of bibliometrics in this research. Thomson Reuters WOS's online database Science Citation Index-Expanded is a valuable tool for collecting and processing data. Therefore, we acquired all studies published from 2012 to 2023 from the database, and the retrieval was completed on November 17th, 2023. For retrieval, the search language was set to English, and then the keyword was set to ferroptosis or ferroptotic OR iron-death. We did not include computer-filtered articles in our study, but filtered them based on their content. In other words, we manually filtered articles that are not relevant to the topic, as shown in **Figure 1**.

Data collection and processing of bibliometric: All publication data (title, keywords, author, country and region of origin, institution, journal of publication, date of publication, H-index, citations, and so on) and gene data (related genes, hub genes, and survival curve information) were extracted from the publications by WXR and SDY. Microsoft Excel 2016, GraphPad Prism 8, VOSviewer version 1.6.12, CiteSpace version 5.6 R5 64-bit, were used to present, analyze, and describe the data.

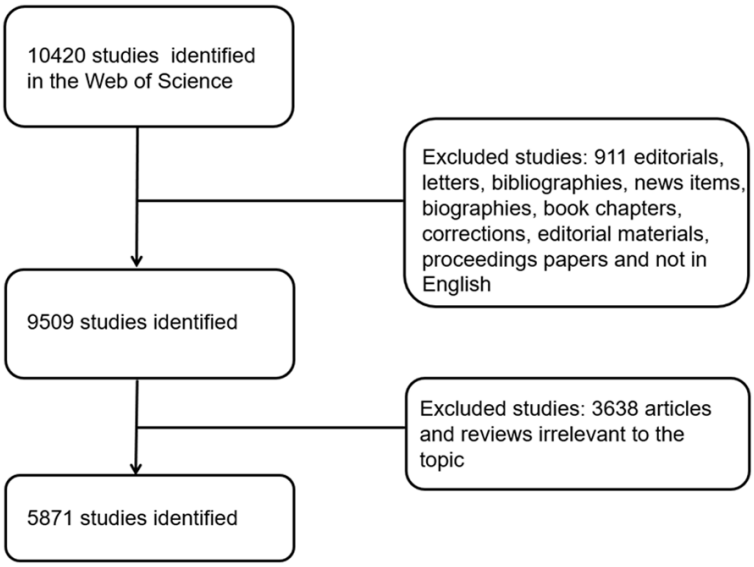


Figure 1. Flow diagram of the inclusion process. The detailed process of screening and enrolment (irrelevant articles were manually excluded by two authors by reading the abstracts and full texts).

Bibliometric analysis: Thomson Reuters Science (WOS) collects a large number of studies, especially those related to biomedicine. Therefore, all included publications were collected from WOS. The website *(https://www.genecards.org)* contains a wealth of genetic information. Using a unique algorithm, it can sequence the genes relevant to the search subject to find the most relevant genes.

H is a useful measure of scientific achievement, which includes factors such as the impact of the number of papers published. Relative research interest (RRI) represents the research interest in a certain field. In this study, the impact factor (IF) was defined by the journal citation report. Especially in recent years, indicators such as H-index, RRI and IF have played an important role in evaluating the scientific research influence of researchers or countries [15].

VOSviewer is a scientific mapping software tool. It is a bibliometric graphics program constructed based on journal co-citation data or keywords and is viewed by authors. It is applied to analyze and visualize keywords in the research and analysis of authors [16]. CiteSpace is an overall network of Java applications. Its main goal is to facilitate the analysis of emerging trends in the field of knowledge and can be used for keyword clustering. It helps summarize a general research direction [15].

Bioinformatics

Data sources and search strategies of bioinformatics: The website (https://www.genecards.org) covered genes related to the aspects of biological processes and diseases. According to different algorithms, the genes related to research topics were screened out, and their correlations were ranked according to the score value. The ranking method is based on the Boolean model and the practical scoring function formula to calculate the value of each gene. In the calculation process, the concepts of the term frequency/inverse document frequency and vector space model are added, as well as modern factors. Based on this, the search term (ferroptosis) is selected and the 40 most relevant genes are obtained.

Data collection and processing of bioinformatics: The Cytoscape version 3.7.1, bibliometrics online analysis platform (http://bibliometric.com/), gene online analysis platform (https://string-db.org/), and tumor prognostic analysis platform (http://gepia.cancer-pku.cn/) were used to present, analyze, and describe the data.

Bioinformatics analysis: Hub genes refer to the genes with a high degree of connectivity within an expression network. Their upstream and downstream pathways involve more genes. Compared to other genes, the upregulation or downregulation of hub genes can cause more changes in the research field [17]. Cytoscape is the software that visualizes the upstream and downstream molecules of biomolecules and related signaling pathways in a grid form, playing a special role in the mining, analysis, and application of genes [18]. The survival curve is one of the most appropriate methods to guide the treatment and diagnosis, to evaluate the prognosis, and to help select the safest and most effective treatment [19].

Results

Bibliometric analysis

A total of 5871 studies from 2012 to 2023 met our inclusion criteria for the bibliometric content. By analyzing and aggregating the data, the contribution of different journals and countries, keywords, contributions of different institutions and related fields are shown in **Figure 2**.

Contributions of countries to global publications: The country, where the first corresponding author was located, was seen as the country to which this article belonged. China has the largest number of publications (3611), accounting for more than half of the total publications (**Figure 3A**). According to the Journal Citation Report of the WOS database, since 2012, all articles related to ferroptosis have been cited 236,124 times, with an average of 45.28 times cited per article. Articles from the United States were cited 48,452 times, ranking the first, accounting for 40.5%, with an H-index of 136 (**Figure 3A**).

By comparing the number of articles published each year, we found that most articles (1756) were published in 2023 (**Figure 3B**). Global interest in ferroptosis measured using RRI increased since 2012 and at its peak in 2022 (**Figure 3B**).

In **Figure 4A** and **4B**, the circle size represents the number of articles, which is consistent with the previous conclusion. Based on the analysis of all elements in **Figure 4**, China and the United States, as the top two countries with the maximum number of publications, conducted the most cooperation in this field.

Contributions of different institutions to publications: Central South University and Zhejiang University ranked first in terms of the number of articles published in this field. Eight of the top 10 institutions in this field are in China (**Figure 5A**). In **Figure 5B** and **5C**, the size of the ball represents the number of publications from this institution. The top three institutions are Central South University, Zhejiang University, and Shanghai Jiao Tong University, and all of them are located in China (**Figure 5B** and **5C**).

Contributions of different journals to publications: **Figure 6A** lists the top 10 journals with the maximum number of articles published on ferroptosis. The maximum number of articles on this topic were published in *Cell Death Disease* (IF = 8.469). The second most was *Biochemical and biophysical Research Communications* (IF = 3.575). *Frontiers in Cell and Developmental Biology* (IF = 6.684) ranked third. In **Figure 6B**, the size of the ball represents the total number of articles published worldwide, which visually shows the difference in the number of articles published by different journals.

Analysis of keywords in publications on the ferroptosis: We extracted keywords from 2637 publications and divided them into 3 clusters for further analysis via VOSviewer. The box in **Figure 7A** and the color block in **Figure 7C** represent the three different clusters of these keywords, namely “Mechanism of Ferroptosis” (red), “Regulation of Ferroptosis” (green), and “Application of Ferroptosis” (blue). As shown in **Figure 7B**, 172 keywords in the 3 fields were frequently mentioned during the analysis, specifically terms that appeared more than 50 times in the titles and abstracts of all articles. The top three keywords were lipid peroxidation model (628 times), model (581 times), and inhibition (522 times). **Figure 7B** shows the detailed data of all the included keywords appearing simultaneously. VOSviewer colored all keywords based on the average time of word occurrence. Specifically, blue indicates that the word appeared relatively early, while yellow indicates that the word appeared relatively late. The latest keyword was RCD (50 times) in cluster 1, FTH1 (50 times) in cluster 2, and nomogram (60 times) in cluster 3. After keyword processing, we found that “nomogram” was the latest of the 172 keywords, which appeared in 2021. From the 172 keywords, we compiled a list of the 15 longest lasting keywords (**Figure 7D**). The most recent keyword that stood out in our study was “chemotherapy”, which was focused on for 2 years from 2019 to 2020; “growth” was focused on for 5 years from 2012 to 2017, which was the longest period. However, since 2019, “chemotherapy” has gradually become the focus of research in this field.

Related field analysis of the ferroptosis: As shown in **Figure 8**, 5871 publications we studied were in one field, including molecular biology and immunology. In addition, the references

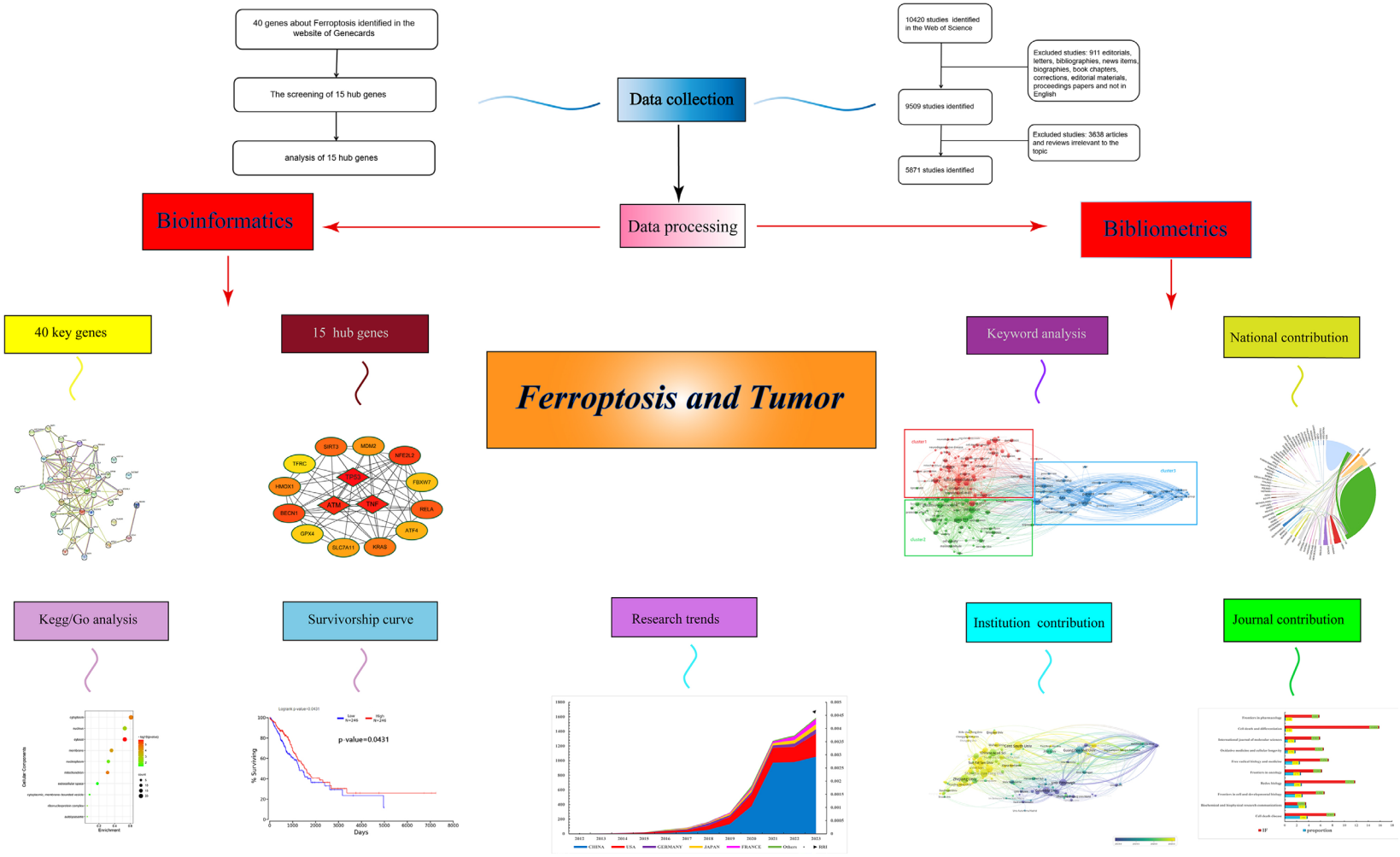


Figure 2. Bibliometrics and bioinformatics analysis flow chart of ferroptosis-related studies.

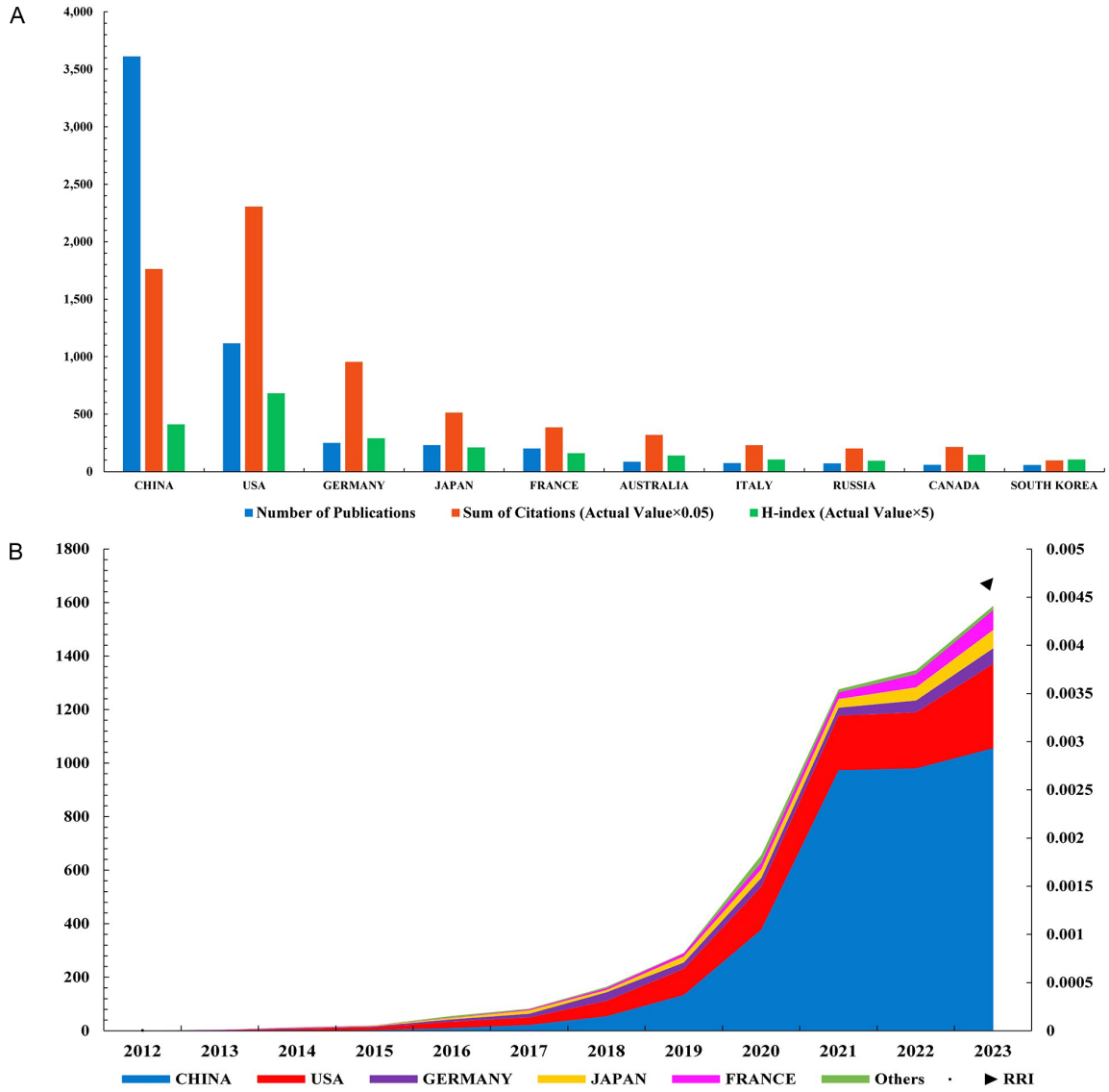


Figure 3. Contribution of different countries to ferroptosis research and the trend of publications. A. Number of publications, sum of citations (×0.05), and H-index (×5) in the top 10 countries or regions. B. Number of publications worldwide and the time course of the RRI on ferroptosis research.

were in one field, including molecular biology and genetics. We found that ferroptosis was mainly related to the basic disciplines of clinical medicine, such as molecular biology, cell biology, and immunology. The development of this field was also related to the basic fields of clinical medicine, such as molecular biology, cell biology, and genetics.

Bioinformatics analysis

The 40 genes most related to ferroptosis were screened on January 4, 2022, and KEGG/GO analysis was conducted on them to analyze the cellular components, molecular functions, biological processes, and signal pathways involved in ferroptosis. We used Cytoscape software to calculate and screen 15 hub genes from the 40 genes. Through the results of literature metrology analysis, we found that the utilizing ferroptosis in chemotherapy and immunotherapy for tumors will be the focus of future research. So, we applied 15 Hub-genes for the tumor analysis. Specific results are shown in **Figure 2**.

KEGG signaling pathway enrichment and GO functional annotation analysis: GO functional annotation and KEGG signaling pathway enrich-

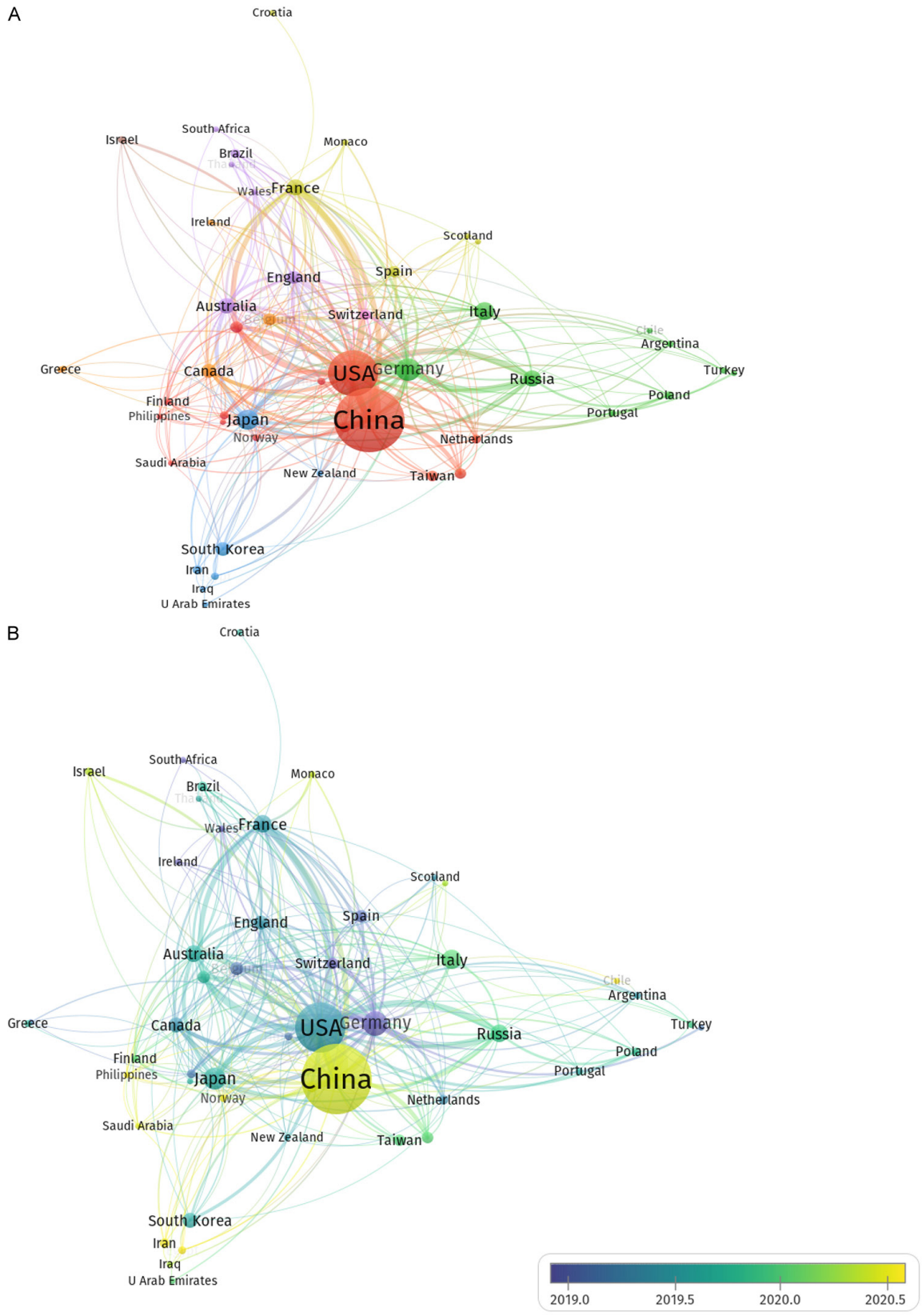


Figure 4. Contribution of different countries to ferroptosis research and cooperative network of countries on ferroptosis research. A. Network of cooperative relations between countries/regions was established using VOSviewer. B. Date of publications and research cooperation network of various countries.

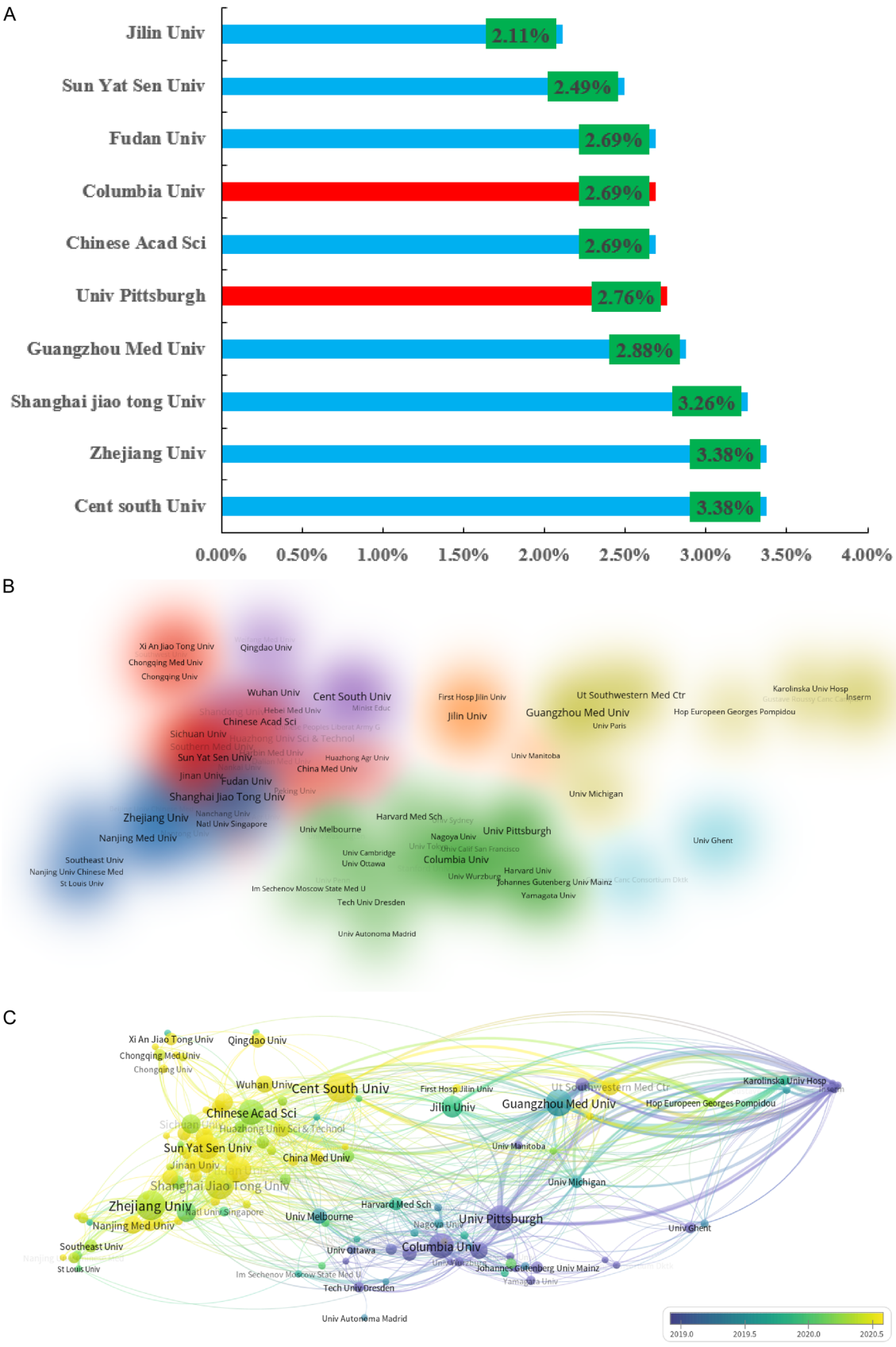


Figure 5. Distribution of institutions engaged in research on ferroptosis. A. Top 10 institutions by the number of publications. Numbers represent the percentage of publications, with blue representing institutions in China and

red representing institutions in the United States. B. Network of institutions produced in VOSviewer. The size of the circles reveals the number of publications. C. Distribution of publications is presented according to the average time of appearance. Blue represents an early appearance, and yellow represents a late appearance.

ment analysis were performed using the online analytical tool David Database to gain a comprehensive understanding of the biological characteristics of ferroptosis. The GO analysis showed that the cellular components of ferroptosis included cytoplasm, nucleus, cytosol, membrane, nucleoplasm, and so forth (**Figure 9A**). The enriched molecular function of ferroptosis involved protein N-terminus binding, protease binding, protein binding, identical protein binding, transcription regulatory region, DNA binding, and so forth (**Figure 9B**). The GO analysis showed that the enriched biological processes of ferroptosis included positive regulation of gene expression, positive regulation of apoptotic process, cellular response to hypoxia, cellular response to hydrogen peroxide, cellular response to glucose starvation, and so forth (**Figure 9C**). The KEGG analysis revealed that the enriched pathways of ferroptosis included microRNAs in cancer, viral carcinogenesis, and so forth (**Figure 9D**).

Top 15 hub genes from the STRING online analysis tool and Cytoscape: The STRING online analysis tool was used for the construction and visualization of gene networks for 40 related genes. Similarly, we also used Cytoscape software to apply its NCC algorithm, and 15 hub genes were screened from the 40 related genes (**Figure 10A**). As shown in **Figure 10A**, the darker the background color, the closer the gene was to the center of the network, indicating its core position in the network. The upregulation or downregulation of these genes led to large changes in the pathway, which impacted the biological effect of ferroptosis. The top three genes and their centricity were as follows: *P53* (2089), *TNF* (1872), and ATM (1753). The 12 hub genes left in the central network from high to low were *NFE2L2*, *BECN1*, *RELA*, *SIRT3*, *KRAS*, *HMOX1*, *MDM2*, *SLC7A11*, *ATF4*, *FBXW7*, *GPX4*, and *TFRC* (**Figure 10B**).

Pan-cancer analysis of 15 hub genes: In bibliometric research, it is predicted that tumors will be a hot field of future development. In bioinformatics analysis, we can realize that most of the signaling pathways involved in related genes are also related to tumors. Therefore, a pan-cancer analysis was conducted for the hub genes related to ferroptosis, and the OncoLnc online analysis platform was used to analyze the expression levels of 15 hub genes of ferroptosis in the top 5 tumors with the highest incidence: lung squamous cell carcinoma, lung adenocarcinoma, breast cancer, colon cancer, and rectal cancer (Supplementary Table 1). We found that high expression of *SIRT3* could improve the prognosis of patients with breast cancer ($P = 0.0408$) (**Figure 11A**); high expression of *GPX4* could improve the prognosis of patients with lung adenocarcinoma ($P = 0$, $P = 0.0431$) (**Figure 11B**); the expression of *TFRC* could improve the prognosis of patients with lung squamous cell carcinoma ($P = 0.042$) (**Figure 11C**). These are all interesting targets for tumor therapy.

Discussion

The concept of ferroptosis was first proposed by Brent R. Stockwell's team in 2012. In recent years, ferroptosis has gained significant attention [20]. Regarding the relationship between ferroptosis and tumor, results of our study from different aspects (miRNA, typical tumor, hub genes, survival curve, and chemotherapy) showed that tumor will be the focal point and core of ferroptosis research in the future, guiding its development direction (**Figure 12**).

The GO analysis of ferroptosis-related genes and the KEGG analysis revealed that the enriched pathways of ferroptosis included microRNAs in cancer, viral carcinogenesis, and so forth (**Figure 9D**). microRNAs in cancer are the hotspot and focus of current research, and the field of ferroptosis has received great attention. The expression of miRNA can be correlated with cancer type, stage, and other clinical variables. More importantly, miRNA can be used as a tool for cancer diagnosis and prognosis [21]. Vasconcelos reported that the overexpression of miRNA-128 decreased the number of acute myeloid leukemia cells and increased DNA damage, which has positive significance for improving the survival rate of patients with cancer, and the process was closely related to ferroptosis [22]. miRNAs also play significant

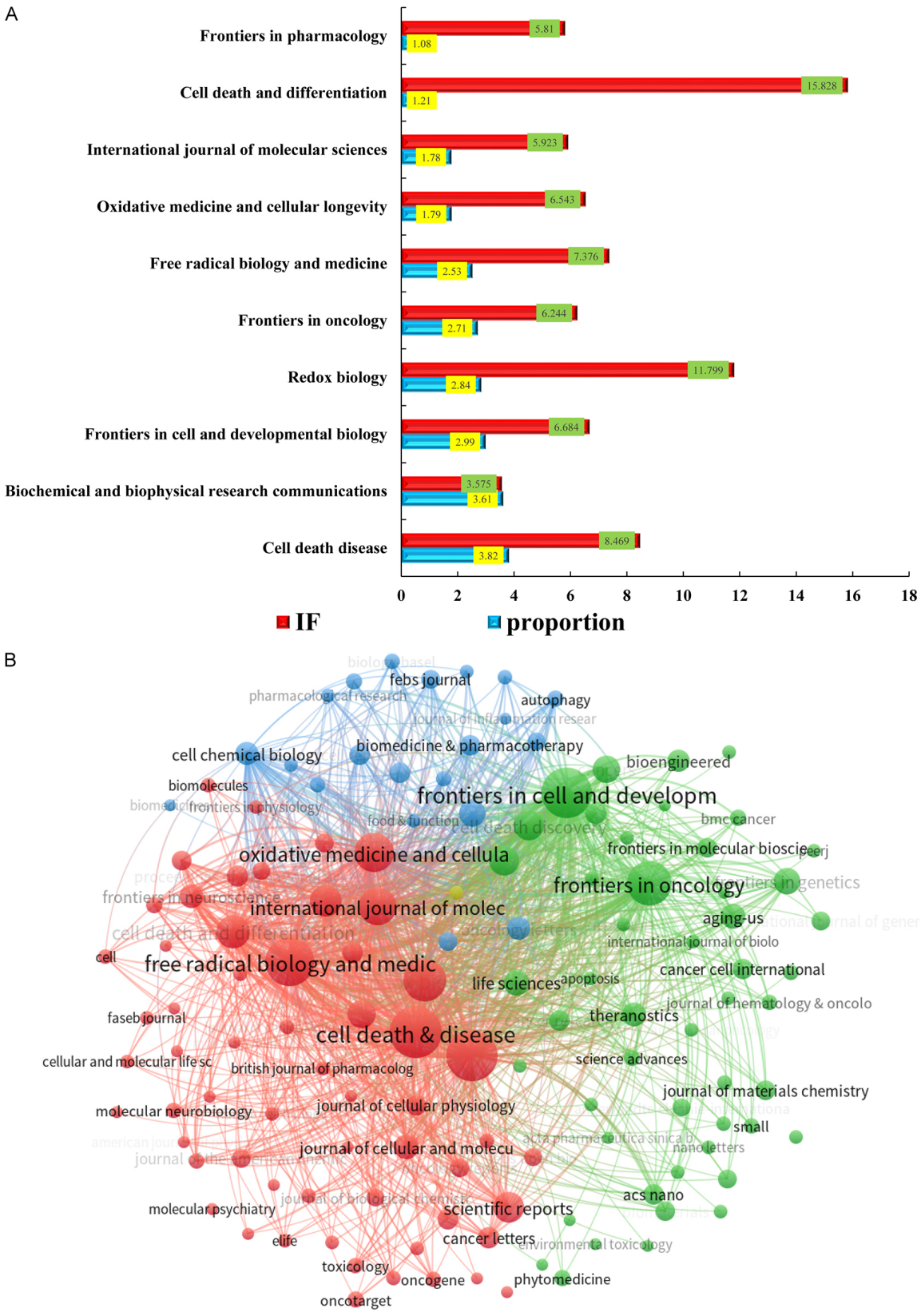
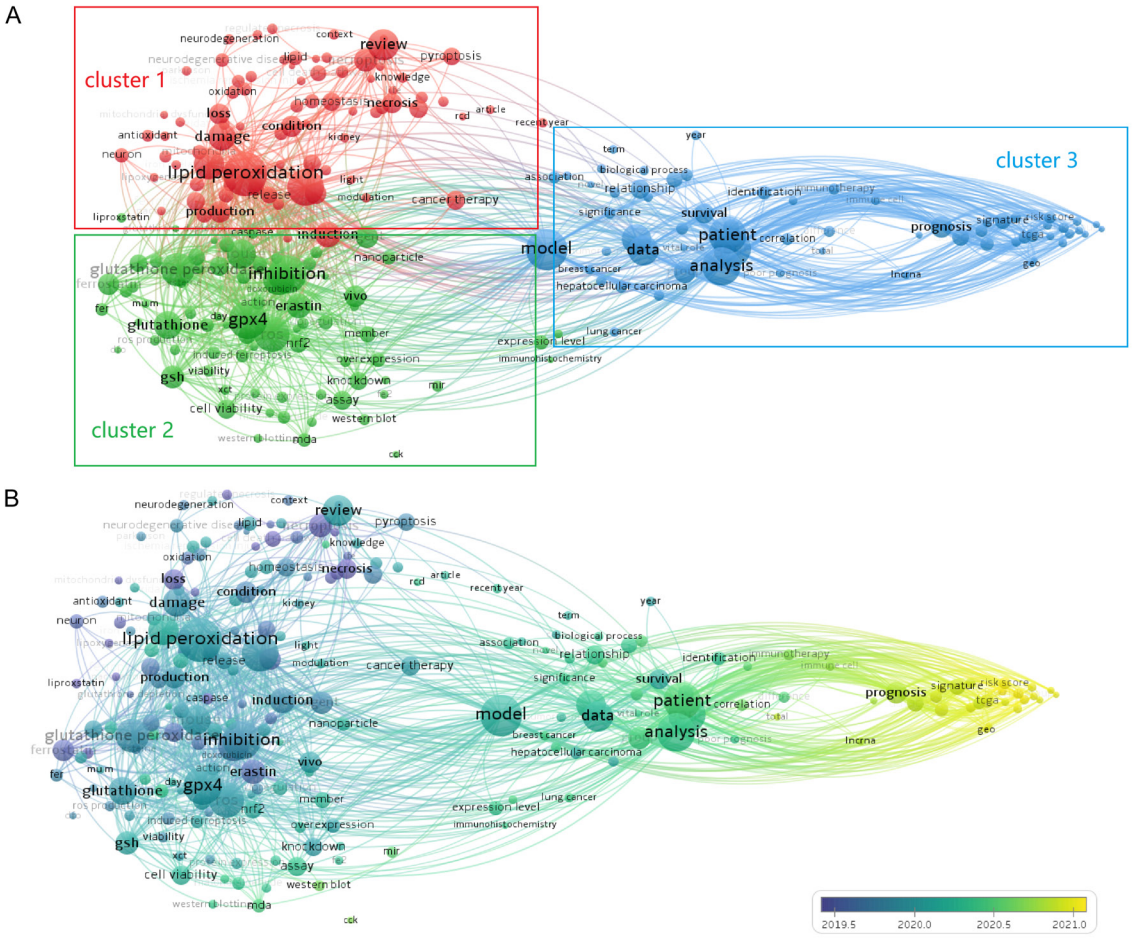


Figure 6. Distribution of journals engaged in research on ferroptosis. A. Top 10 journals by the number of publications, with blue bar representing the proportion and red bar representing IF. B. Network of institutions produced in VOSviewer.


A
cluster 1
cluster 2
cluster 3
review
pyroptosis
necrosis
lipid peroxidation
damage
condition
antioxidant
neuron
oxidation
loss
production
release
light
modulation
cancer therapy
induction
nanoparticle
inhibition
erastin
vivo
gpx4
glutathione
glutathione peroxidase
nrf2
overexpression
knockdown
gsh
viability
cell viability
assay
western blot
mda
mir
model
data
analysis
patient
survival
prognosis
signature
risk score
tcga
geo
lncrna
correlation
identification
relationship
significance
hepatocellular carcinoma
breast cancer
lung cancer
expression level
immunohistochemistry
B
2019.5
2020.0
2020.5
2021.0
C
ferroptosis
ferroptosis inhibitor
ferroptotic cell death
reactive oxygen species
fenton reaction
tumor
tumor microenvironment
immunotherapy
progression
chemotherapy
metastasis
group
poor prognosis
gene expression
tcgalow risk group
database

D

Top 15 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2012 - 2020
growth	2012	2.48	**2012**	2017	
apoptosis	2012	2.43	**2014**	2015	
mice	2012	4.54	**2015**	2018	
in vivo	2012	2.65	**2015**	2018	
ra	2012	2.53	**2015**	2016	
nonapoptotic cell death	2012	7.61	**2016**	2018	
expression	2012	4.05	**2016**	2017	
resistance	2012	3.57	**2016**	2017	
inhibitor	2012	2.92	**2016**	2018	
tumor suppression	2012	2.85	**2016**	2018	
vitamin e	2012	3.15	**2017**	2017	
oxidativestress	2012	2.77	**2017**	2018	
cystine/glutamate antiporter	2012	2.97	**2018**	2020	
derivative	2012	2.33	**2018**	2020	
chemotherapy	2012	2.45	**2019**	2020	

Figure 7. Co-occurrence analysis of all keywords in the publications on ferroptosis research. A. Grouping of keywords in the field of ferroptosis. B. Mapping of the keywords in the field of ferroptosis. The size of the circle represents the frequency at which keywords appeared. The distribution of keywords is presented according to the average time of appearance. Blue represents an early appearance, while yellow represents a late appearance. C. Grouping of keywords in the field of ferroptosis research. D. Top 15 keywords cited the most from 2012 to 2021 and received continuous attention for a certain period. The red bars represent frequently cited keywords during this period. The green bars represent infrequently cited keywords.

roles from almost all aspects of cancer biology, such as proliferation, apoptosis, invasion/metastasis, and angiogenesis [21]. Targeted miRNA provided us with new ideas for angiogenesis-related tumor therapy by influencing drug delivery [23]. Examples of pro-angiogenic miRNAs are miR-9 or miR-494, often overexpressed in tumors, inducing migration and angiogenesis. The process is closely related to the production of ROS, which is of great significance to the degree of vascular injury [24]. Similarly, research has also demonstrated that tumor suppressor mir-424-5p can eliminate iron cell apoptosis in ovarian cancer by targeting long-chain-fatty-acid--CoA ligase 4 (ACSL4), providing directions for the treatment of ovarian cancer [25]. The same area of viral carcinogenesis has also received attention. The World Health Organization currently estimates that approximately 22% of worldwide cancers are attributable to infectious etiologies, of which viral etiologies are estimated at 15%-20% [26]. Therefore, the inhibition of viral activity is particularly important in tumorigenesis. Studies have shown that FADS2-dependent fatty acid desaturation plays a crucial role in determining cellular sensitivity to ferroptosis and permissiveness for hepatitis C virus replication during ferroptosis, and this process is implicated in reducing the incidence of liver cancer [27]. Similarly, studies have shown that these possibilities are largely affected by the virus-killing effects of the immune cells associated with ferroptosis [26]. HLA-DR expression on proliferating CD8+ T cells is the core mechanism of hepatitis C virus clearance [28], which is a milestone in our understanding of antiviral therapy for cancer.

SIRT3 is an important regulator of ferroptosis, because its deficiency induces resistance to autophagy-dependent ferroptosis [29]. In addi-

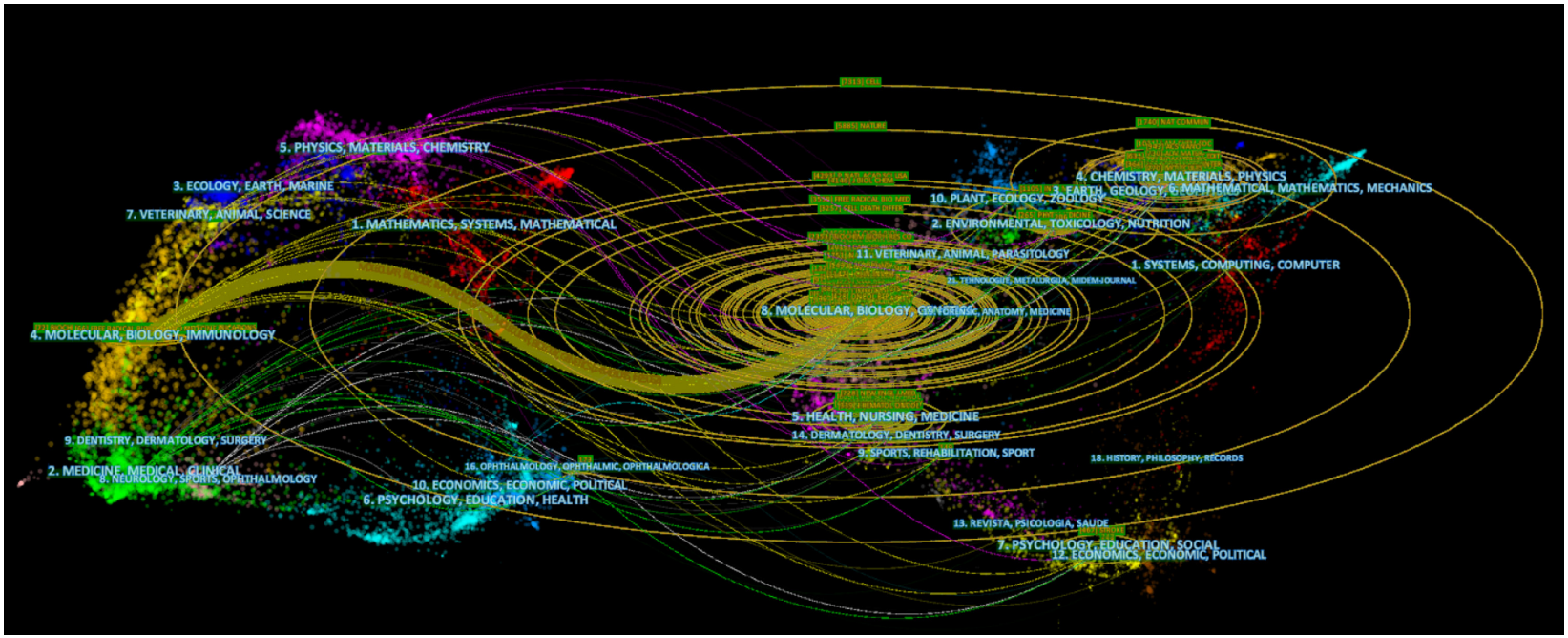


Figure 8. Related fields of ferroptosis. The left side represents the fields of articles included in the study, and the right side represents the fields of references of articles.

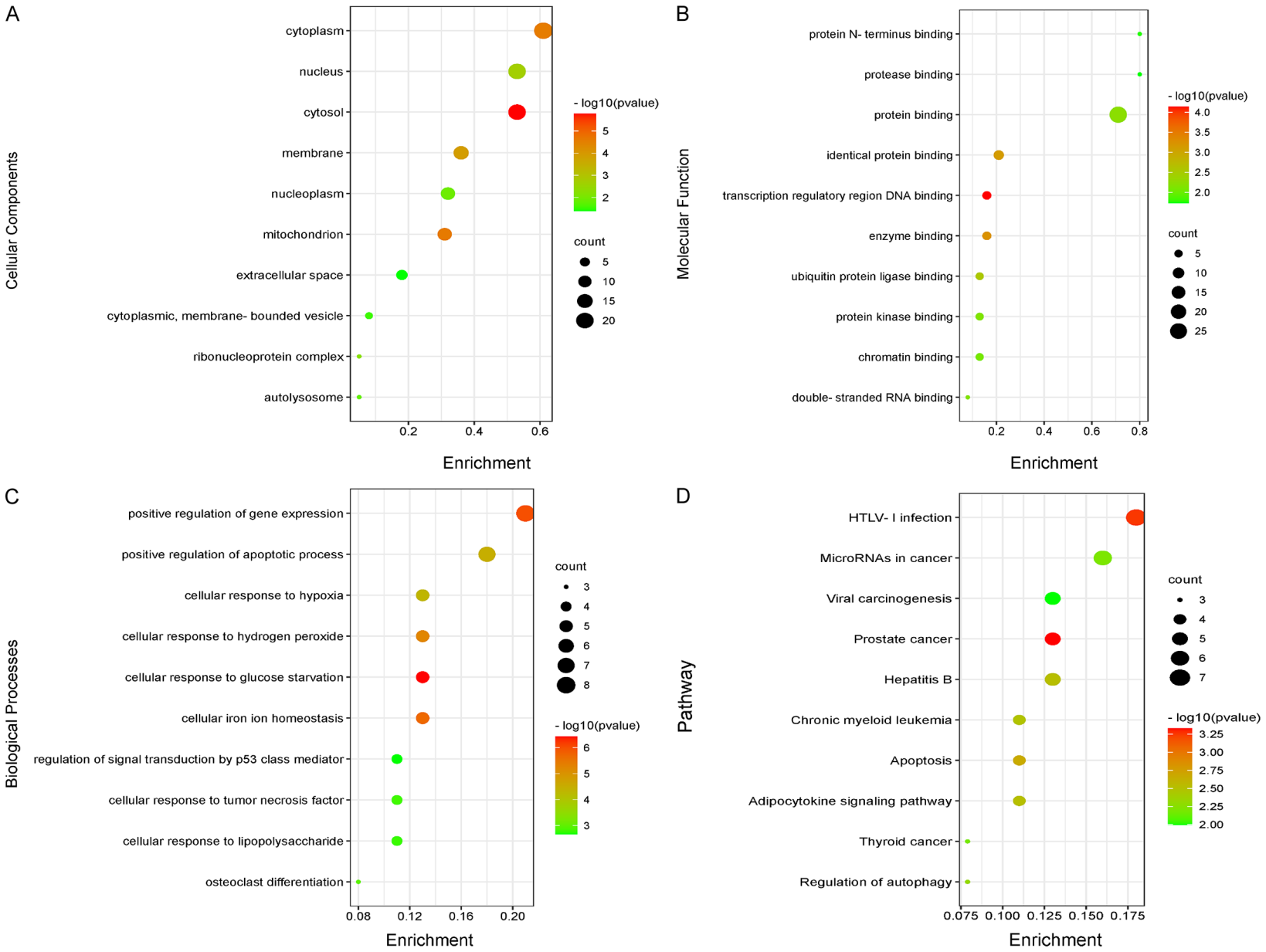

A
Cellular Components
cytoplasm
nucleus
cytosol
membrane
nucleoplasm
mitochondrion
extracellular space
cytoplasmic, membrane- bounded vesicle
ribonucleoprotein complex
autolysosome
0.2
0.4
0.6
Enrichment
- log10(pvalue)
5
4
3
2
count
5
10
15
20
B
Molecular Function
protein N- terminus binding
protease binding
protein binding
identical protein binding
transcription regulatory region DNA binding
enzyme binding
ubiquitin protein ligase binding
protein kinase binding
chromatin binding
double- stranded RNA binding
0.2
0.4
0.6
0.8
Enrichment
- log10(pvalue)
4.0
3.5
3.0
2.5
2.0
count
5
10
15
20
25
C
Biological Processes
positive regulation of gene expression
positive regulation of apoptotic process
cellular response to hypoxia
cellular response to hydrogen peroxide
cellular response to glucose starvation
cellular iron ion homeostasis
regulation of signal transduction by p53 class mediator
cellular response to tumor necrosis factor
cellular response to lipopolysaccharide
osteoclast differentiation
0.08
0.12
0.16
0.20
Enrichment
count
3
4
5
6
7
8
- log10(pvalue)
6
5
4
3
D
Pathway
HTLV- I infection
MicroRNAs in cancer
Viral carcinogenesis
Prostate cancer
Hepatitis B
Chronic myeloid leukemia
Apoptosis
Adipocytokine signaling pathway
Thyroid cancer
Regulation of autophagy
0.075
0.100
0.125
0.150
0.175
Enrichment
count
3
4
5
6
7
- log10(pvalue)
3.25
3.00
2.75
2.50
2.25
2.00

Figure 9. GO and KEGG analysis of ferroptosis. A. GO analysis (cellular components) of genes associated with ferroptosis. B. GO analysis (molecular function) of genes associated with ferroptosis. C. GO analysis (biological processes) of genes associated with ferroptosis. D. KEGG analysis (pathway) of genes associated with ferroptosis.

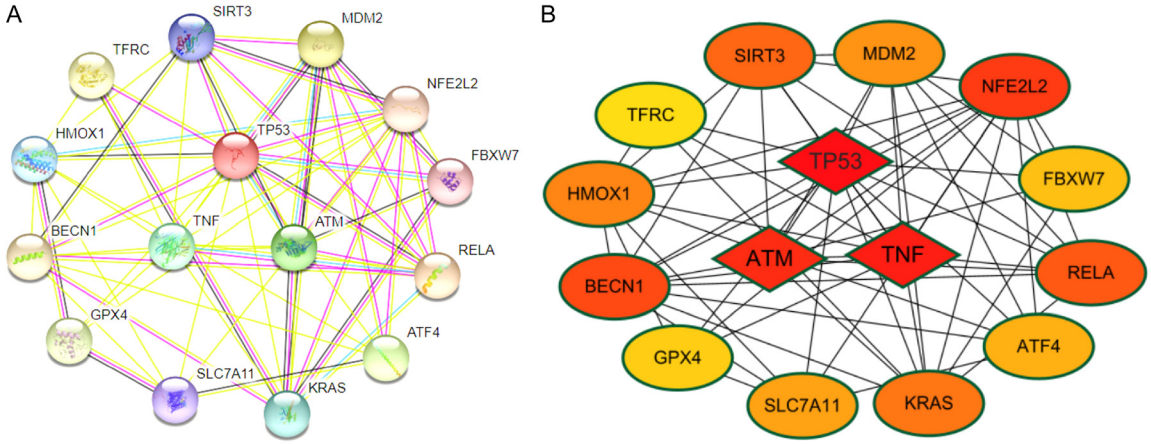


Figure 10. Important genes of ferroptosis. A. Fifteen hub-genes from CytoScope. B. PPI network of the top 15 hub genes.

tion, mechanistic studies showed that *SIRT3* expression promoted the activation of the AMPK-mTOR pathway and reduced the level of glutathione peroxidase 4 (GPX4), thereby increasing autophagy and ferroptosis [29]. In some types of cancers, *SIRT3* functions as a tumor promoter, since it keeps ROS levels under a certain threshold compatible with cell viability and proliferation. However, this does not fully account for the positive tumor-promoting effect. On the contrary, other studies describe *SIRT3* as a tumor suppressor, as it can trigger cell death under stress conditions, which has a certain killing effect on tumor cells [29]. However, in our study, *SIRT3* was found to have a significant effect on the prognosis of breast cancer (**Figure 11A**). Similar to the results of our analysis, oroxylin A inhibited glycolysis-dependent proliferation of breast cancer cells through the suppression of HIF-1α stabilization via *SIRT3* activation, providing the basis for the cancer therapies involving the stimulation of *SIRT3* [30]. However, the role of this gene in other tumors still needs to be explored. As a selenoprotein, GPX4 protein has the characteristics of low synthesis efficiency and high energy. It suppresses lipid peroxidation with glutathione (GSH) and plays an important role in inhibiting iron toxicity [31]. Some studies have shown that, in tumor treatment, the activation of the mTORC1 target promotes its production. Therefore, mTORC1 inhibitor and iron inducer combined therapy may be a new method [1]. Furthermore, we found that the antitumor mechanisms were more complex for specific tumors. For lung adenocarcinoma, tumors with a higher degree of malignancy were more likely to have a low degree of lipid peroxidation, which directly determined the stage and grade of the tumor. Previous research showed that targeting this cAMP response element-binding protein/E1A-binding protein P300/GPX4 axis might play a key role in oxidative stress and provide new strategies for treating lung adenocarcinoma [32]. This finding is consistent with our analysis of the survival rate of patients with lung adenocarcinoma caused by this gene difference (**Figure 11B**). TFRC m6A methylation, as a currently recognized iron metabolism-dependent process, plays an important role in ferroptosis [33]. The expression of Yes associated protein (YAP) is enhanced and stabilized by O-GlcNAcylation, and, in terms of antitumor activity, O-GlcNAcylation can increase the iron content of tumor cells via YAP/TFRC. It can provide a new basis for developing clinical treatment strategies for patients with cancers, especially liver cancer [34]. Studies have shown that oral cancer patients with the positive results of TFRC mRNA displayed a significantly worse prognosis than those with negative prognostic

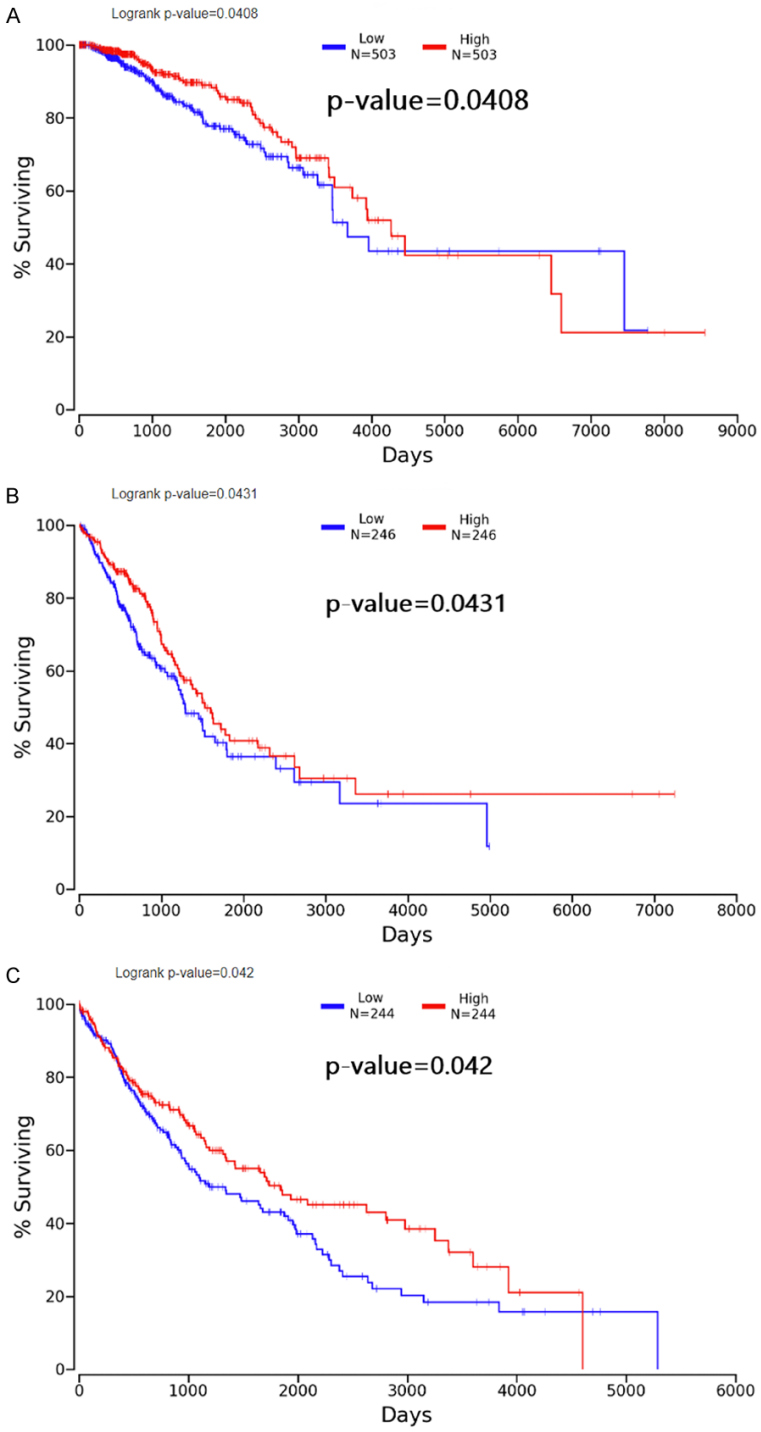


Figure 11. Relationship between hub-gene expression and survival rate of tumor patients. A. Effect of the SIRT3 expression level on the prognosis of breast cancer (P = 0.0408). B. Effect of the GPX4 expression level on the prognosis of lung adenocarcinoma (P = 0.0431). C. Effect of the TFRC expression level on the prognosis of lung squamous cell carcinoma (P = 0.042).

results [35]. Our study found that it had a more obvious effect on the prognosis of lung squamous cell carcinoma (**Figure 11C**). However, the prognostic effect of genes on patients with respiratory tumors is still not clear, so the role of this gene in this field remains to be explored. We believe that the three hub genes in ferroptosis, *SIRT3*, *GPX4*, and *TFRC*, are of great significance in the antitumor process and may also receive more attention.

It is not the purpose of bibliometrics and bioinformatics in the traditional sense to collate and summarize these 8642 articles manually. This supplementary work is intended to facilitate the reader's access to full knowledge about the relationship between ferroptosis and tumors in a more effective way. Through manual literature analysis, the immunotherapy of tumors was found to be a hot topic in the current research. The related substances of ferroptosis have strong immunogenicity, and ferroptosis itself can be thought of as a proinflammatory process [19]. A study found that iron ions could recruit and activate the function of immune cells at the tumor site through chemotactic signaling, suggesting that iron ion antagonists may emerge as a form of antitumor immune therapy [30] and open up a wider domain for tumor treatment. Current studies have linked ferroptosis to the tumor microenvironment (TME), indicating the roles of ferroptosis are not only in immune cells in the TME but also in the crosstalk between tumor cells and immune cells, especially in the immune regulation of prostate cancer [36]. Although it is not clear when tumor immune cells need to be protected from damage and

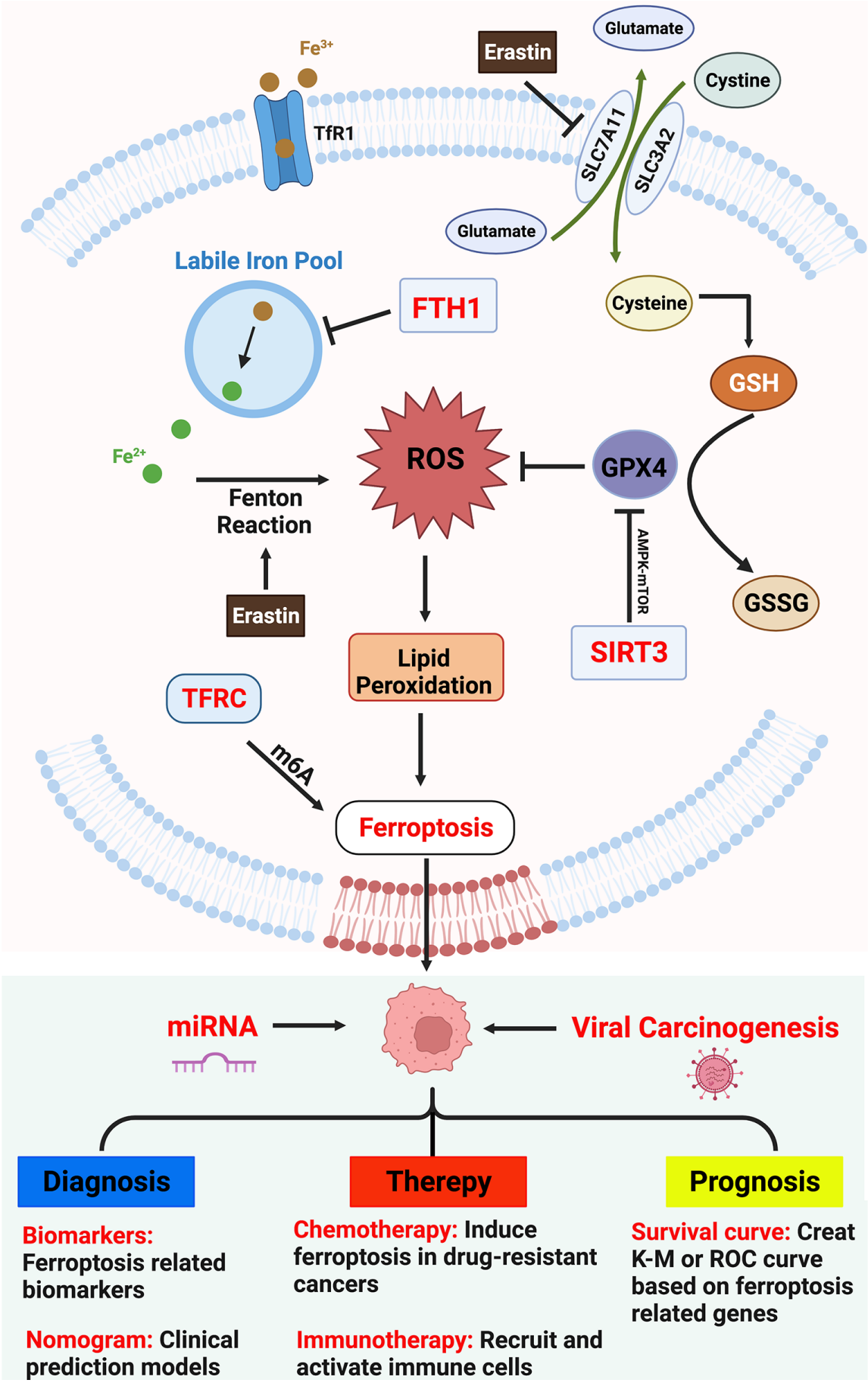

Fe3+
TfR1
Erastin
Glutamate
Cystine
SLC7A11
SLC3A2
Glutamate
Labile Iron Pool
FTH1
Cysteine
GSH
Fe2+
Fenton Reaction
ROS
GPX4
AMPK-mTOR
GSSG
Erastin
Lipid Peroxidation
SIRT3
TFRC
m6A
Ferroptosis
miRNA
Viral Carcinogenesis
Diagnosis
Therepy
Prognosis
Biomarkers: Ferroptosis related biomarkers
Nomogram: Clinical prediction models
Chemotherapy: Induce ferroptosis in drug-resistant cancers
Immunotherapy: Recruit and activate immune cells
Survival curve: Creat K-M or ROC curve based on ferroptosis related genes

Figure 12. Mechanism of ferroptosis and its role in cancer research. The occurrence process and internal mechanism of ferroptosis, in which reactive oxygen species plays an important role, and ferroptosis plays an important role in the diagnosis, treatment, and prognosis of tumors.

when their function should be suppressed, research in this area may provide a perspective on targeting ferroptosis in cancer immunotherapy.

We believe that the research on ferroptosis in the field of cancer will receive more attention and experience significant development amidst a rapidly increasing number of articles published. After a comprehensive analysis of the research trend in the whole field, we find that the research in this field may gradually receive more attention in the future through RRI (**Figure 3B**). Different countries, institutions, and organizations, as well as top publications, have contributed to the development of this field.

Limitations

This study surveyed publications from the WOS database to obtain objective and reliable results. However, our results might differ slightly from the real-time results due to the limitation of the search for English studies and the constant updating of the database. For more comprehensive results, we can use Medline, Scopus, Google Scholar and other databases for comparison in further studies. Attention should also be given to other types of publications and publications in other languages.

Conclusion

China has contributed the maximum number of publications to ferroptosis research, which is inseparable from the contribution of the national institutions. The cooperation among countries and disciplines is crucial. According to the RRI, we expect the total number of global publications to grow in the future. Importantly, “RCD”, “FTH1”, and “nomogram” may be the hot spots for future research. The 40 genes associated with ferroptosis play a key role in the expression of microRNAs in cancer and viral carcinogenesis pathway. Tumor immunotherapy and chemotherapy will also be the future research hotspots in this field. Hub genes, such as *SIRT3*, *GPX4*, and *TFRC*, are significant in the antitumor process.

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Disclosure of conflict of interest

None.

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References

[1] Zhang Y, Swanda RV, Nie L, Liu X, Wang C, Lee H, Lei G, Mao C, Koppula P, Cheng W, Zhang J, Xiao Z, Zhuang L, Fang B, Chen J, Qian SB and Gan B. mTORC1 couples cyst(e)ine availability with GPX4 protein synthesis and ferroptosis regulation. Nat Commun 2021; 12: 1589.

[2] Stockwell BR, Jiang X and Gu W. Emerging mechanisms and disease relevance of ferroptosis. Trends Cell Biol 2020; 30: 478-490.

[3] Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison B 3rd and Stockwell BR. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012; 149: 1060-1072.

[4] Xu T, Ding W, Ji X, Ao X, Liu Y, Yu W and Wang J. Molecular mechanisms of ferroptosis and its role in cancer therapy. J Cell Mol Med 2019; 23: 4900-4912.

[5] Riegman M, Sagie L, Galed C, Levin T, Steinberg N, Dixon SJ, Wiesner U, Bradbury MS, Ni-

ethammer P, Zaritsky A and Overholtzer M. Ferroptosis occurs through an osmotic mechanism and propagates independently of cell rupture. Nat Cell Biol 2020; 22: 1042-1048.
[6] Akalin PK. Introduction to bioinformatics. Mol Nutr Food Res 2006; 50: 610-619.
[7] Jiang X, Stockwell BR and Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol 2021; 22: 266-282.
[8] Chandra SP, Singh A, Goyal N, Laythalling RK, Singh M, Kale SS, Sharma MS, Suri A, Singh P, Garg A, Sarkar C, Tripathi M, Sharma BS and Mahapatra AK. Analysis of changing paradigms of management in 179 patients with spinal tuberculosis over a 12-year period and proposal of a new management algorithm. World Neurosurg 2013; 80: 190-203.
[9] Rad AE, Brinjikji W, Cloft HJ and Kallmes DF. The H-index in academic radiology. Acad Radiol 2010; 17: 817-821.
[10] Chen X, Kang R, Kroemer G and Tang D. Ferroptosis in infection, inflammation, and immunity. J Exp Med 2021; 218: e20210518.
[11] Hassannia B, Vandenabeele P and Vanden Berghe T. Targeting ferroptosis to iron out cancer. Cancer Cell 2019; 35: 830-849.
[12] Li D and Li Y. The interaction between ferroptosis and lipid metabolism in cancer. Signal Transduct Target Ther 2020; 5: 108.
[13] Wang W, Green M, Choi JE, Gijon M, Kennedy PD, Johnson JK, Liao P, Lang X, Kryczek I, Sell A, Xia H, Zhou J, Li G, Li J, Li W, Wei S, Vatan L, Zhang H, Szeliga W, Gu W, Liu R, Lawrence TS, Lamb C, Tanno Y, Cieslik M, Stone E, Georgiou G, Chan TA, Chinnaiyan A and Zou W. CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy. Nature 2019; 569: 270-274.
[14] Eyre-Walker A and Stoletzki N. The assessment of science: the relative merits of post-publication review, the impact factor, and the number of citations. PLoS Biol 2013; 11: e1001675.
[15] Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, Annicchiarico-Petruzzelli M, Antonov AV, Arama E, Baehrecke EH, Barlev NA, Bazan NG, Bernassola F, Bertrand MJM, Bianchi K, Blagosklonny MV, Blomgren K, Borner C, Boya P, Brenner C, Campanella M, Candi E, Carmona-Gutierrez D, Cecconi F, Chan FK, Chandel NS, Cheng EH, Chipuk JE, Cidlowski JA, Ciechanover A, Cohen GM, Conrad M, Cubillos-Ruiz JR, Czabotar PE, D'Angiolella V, Dawson TM, Dawson VL, De Laurenzi V, De Maria R, Debatin KM, DeBerardinis RJ, Deshmukh M, Di Daniele N, Di Virgilio F, Dixit VM, Dixon SJ, Duckett CS, Dynlacht BD, El-Deiry WS, Elrod JW, Fimia GM, Fulda S, Garcia-Saez AJ, Garg AD, Garrido C, Gavathiotis E, Golstein P, Gottlieb E, Green DR, Greene LA, Gronemeyer H, Gross A, Hajnoczky G, Hardwick JM, Harris IS, Hengartner MO, Hetz C, Ichijo H, Jaattela M, Joseph B, Jost PJ, Juin PP, Kaiser WJ, Karin M, Kaufmann T, Kepp O, Kimchi A, Kitsis RN, Klionsky DJ, Knight RA, Kumar S, Lee SW, Lemasters JJ, Levine B, Linkermann A, Lipton SA, Lockshin RA, Lopez-Otin C, Lowe SW, Luedde T, Lugli E, MacFarlane M, Madeo F, Malewicz M, Malorni W, Manic G, Marine JC, Martin SJ, Martinou JC, Medema JP, Mehlen P, Meier P, Melino S, Miao EA, Molkentin JD, Moll UM, Munoz-Pinedo C, Nagata S, Nunez G, Oberst A, Oren M, Overholtzer M, Pagano M, Panaretakis T, Pasparakis M, Penninger JM, Pereira DM, Pervaiz S, Peter ME, Piacentini M, Pinton P, Prehn JHM, Puthalakath H, Rabinovich GA, Rehm M, Rizzuto R, Rodrigues CMP, Rubinsztein DC, Rudel T, Ryan KM, Sayan E, Scorrano L, Shao F, Shi Y, Silke J, Simon HU, Sistigu A, Stockwell BR, Strasser A, Szabadkai G, Tait SWG, Tang D, Tavernarakis N, Thorburn A, Tsujimoto Y, Turk B, Vanden Berghe T, Vandenabeele P, Vander Heiden MG, Villunger A, Virgin HW, Vousden KH, Vucic D, Wagner EF, Walczak H, Wallach D, Wang Y, Wells JA, Wood W, Yuan J, Zakeri Z, Zhivotovsky B, Zitvogel L, Melino G and Kroemer G. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ 2018; 25: 486-541.
[16] Xie L, Chen Z, Wang H, Zheng C and Jiang J. Bibliometric and visualized analysis of scientific publications on atlantoaxial spine surgery based on Web of Science and VOSviewer. World Neurosurg 2020; 137: 435-442, e434.
[17] Liu G, Luo S, Lei Y, Wu J, Huang Z, Wang K, Yang P and Huang X. A nine-hub-gene signature of metabolic syndrome identified using machine learning algorithms and integrated bioinformatics. Bioengineered 2021; 12: 5727-5738.
[18] Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B and Ideker T. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003; 13: 2498-2504.
[19] Djulbegovic B and Guyatt GH. Progress in evidence-based medicine: a quarter century on. Lancet 2017; 390: 415-423.
[20] Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, Brown LM, Girotti AW, Cornish VW, Schreiber SL and Stockwell BR. Regulation of ferroptotic cancer cell death by GPX4. Cell 2014; 156: 317-331.
[21] Lee YS and Dutta A. MicroRNAs in cancer. Annu Rev Pathol 2009; 4: 199-227.

[22] Tutar Y. miRNA and cancer; computational and experimental approaches. Curr Pharm Biotechnol 2014; 15: 429.
[23] Tiwari A, Mukherjee B and Dixit M. MicroRNA key to angiogenesis regulation: miRNA biology and therapy. Curr Cancer Drug Targets 2018; 18: 266-277.
[24] Orso F, Quirico L, Dettori D, Coppo R, Virga F, Ferreira LC, Paoletti C, Baruffaldi D, Penna E and Taverna D. Role of miRNAs in tumor and endothelial cell interactions during tumor progression. Semin Cancer Biol 2020; 60: 214-224.
[25] Ma LL, Liang L, Zhou D and Wang SW. Tumor suppressor miR-424-5p abrogates ferroptosis in ovarian cancer through targeting ACSL4. Neoplasma 2021; 68: 165-173.
[26] Smith AJ and Smith LA. Viral carcinogenesis. Prog Mol Biol Transl Sci 2016; 144: 121-168.
[27] Yamane D, Hayashi Y, Matsumoto M, Nakanishi H, Imagawa H, Kohara M, Lemon SM and Ichi I. FADS2-dependent fatty acid desaturation dictates cellular sensitivity to ferroptosis and permissiveness for hepatitis C virus replication. Cell Chem Biol 2022; 29: 799-810, e4.
[28] Zubkova I, Duan H, Wells F, Mostowski H, Chang E, Pirollo K, Krawczynski K, Lanford R and Major M. Hepatitis C virus clearance correlates with HLA-DR expression on proliferating CD8+ T cells in immune-primed chimpanzees. Hepatology 2014; 59: 803-813.
[29] Han D, Jiang L, Gu X, Huang S, Pang J, Wu Y, Yin J and Wang J. SIRT3 deficiency is resistant to autophagy-dependent ferroptosis by inhibiting the AMPK/mTOR pathway and promoting GPX4 levels. J Cell Physiol 2020; 235: 8839-8851.
[30] Wei L, Zhou Y, Qiao C, Ni T, Li Z, You Q, Guo Q and Lu N. Oroxylin A inhibits glycolysis-dependent proliferation of human breast cancer via promoting SIRT3-mediated SOD2 transcription and HIF1α destabilization. Cell Death Dis 2015; 6: e1714.
[31] Conrad M, Kagan VE, Bayir H, Pagnussat GC, Head B, Traber MG and Stockwell BR. Regulation of lipid peroxidation and ferroptosis in diverse species. Genes Dev 2018; 32: 602-619.
[32] Wang Z, Zhang X, Tian X, Yang Y, Ma L, Wang J and Yu Y. CREB stimulates GPX4 transcription to inhibit ferroptosis in lung adenocarcinoma. Oncol Rep 2021; 45: 88.
[33] Ye J, Wang Z, Chen X, Jiang X, Dong Z, Hu S, Li W, Liu Y, Liao B, Han W, Shen J and Xiao M. YTHDF1-enhanced iron metabolism depends on TFRC m(6)A methylation. Theranostics 2020; 10: 12072-12089.
[34] Zhu G, Murshed A, Li H, Ma J, Zhen N, Ding M, Zhu J, Mao S, Tang X, Liu L, Sun F, Jin L and Pan Q. O-GlcNAcylation enhances sensitivity to RSL3-induced ferroptosis via the YAP/TFRC pathway in liver cancer. Cell Death Discov 2021; 7: 83.
[35] Wada S, Noguchi T, Takeno S and Kawahara K. PIK3CA and TFRC located in 3q are new prognostic factors in esophageal squamous cell carcinoma. Ann Surg Oncol 2006; 13: 961-966.
[36] Hwang HW, Jung H, Hyeon J, Park YH, Ahn JS, Im YH, Nam SJ, Kim SW, Lee JE, Yu JH, Lee SK, Choi M, Cho SY and Cho EY. A nomogram to predict pathologic complete response (pCR) and the value of tumor-infiltrating lymphocytes (TILs) for prediction of response to neoadjuvant chemotherapy (NAC) in breast cancer patients. Breast Cancer Res Treat 2019; 173: 255-266.

Supplementary Table 1. The analytic consequence of 172 keywords with at least 50 occurrence times

Label	Cluster	Occurrences	Average appearing years (AAY)
Regulated necrosis	1	73	2018.6027
Lipoxygenase	1	56	2019.3393
Necroptosis	1	248	2019.375
Necrosis	1	193	2019.399
Cell death pathway	1	136	2019.4191
Discovery	1	97	2019.433
Caspase	1	79	2019.4937
Mitochondrial dysfunction	1	54	2019.5185
Lipid hydroperoxide	1	62	2019.5323
Loss	1	201	2019.5323
Protection	1	90	2019.5444
Importance	1	91	2019.5495
Neuron	1	117	2019.5983
Compound	1	221	2019.6244
Enzyme	1	162	2019.6728
Ferroptotic cell death	1	175	2019.6914
Cell survival	1	62	2019.6935
Reactive oxygen species	1	383	2019.7311
Acute kidney injury	1	66	2019.7424
Condition	1	216	2019.7593
Recent advance	1	52	2019.7692
Neurodegeneration	1	74	2019.7703
Generation	1	148	2019.777
Understanding	1	177	2019.7797
Stress	1	161	2019.7826
Iron dependent accumulation	1	62	2019.7903
Brain	1	100	2019.8
Toxicity	1	120	2019.8
Degradation	1	145	2019.8207
Pyroptosis	1	157	2019.8217
Induction	1	287	2019.8362
Ferritin	1	99	2019.8485
Iron chelator	1	67	2019.8507
Parkinson	1	67	2019.8507
Synthesis	1	138	2019.8551
Neurodegenerative disease	1	114	2019.8596
Endoplasmic reticulum	1	53	2019.8868
Damage	1	327	2019.9052
Production	1	221	2019.9095
Implication	1	111	2019.9099
Release	1	153	2019.9216
Exposure	1	132	2019.9242
Oxidative Damage	1	86	2019.9302
Kidney	1	63	2019.9524
Oxidative stress	1	367	2019.9728
Lipid peroxidation	1	628	2019.9904

Cancer therapy	1	186	2019.9946
Attention	1	88	2020
Hallmark	1	77	2020
Lipid	1	116	2020
Mitochondrium	1	67	2020.0149
Review	1	378	2020.0185
Liver	1	79	2020.0253
Iron dependent lipid peroxidation	1	72	2020.0278
Involvement	1	103	2020.0291
Iron homeostasis	1	113	2020.0354
Stroke	1	82	2020.0366
Field	1	78	2020.0385
Mitochondria	1	119	2020.042
Peroxidation	1	116	2020.0431
Alzheimer	1	69	2020.058
Inflammation	1	170	2020.0706
Ferritinophagy	1	63	2020.0794
Ischemia reperfusion injury	1	98	2020.0918
Injury	1	370	2020.1459
Iron accumulation	1	128	2020.1719
Light	1	62	2020.1774
Prevention	1	78	2020.1923
Iron overload	1	116	2020.2069
Fenton reaction	1	61	2020.2131
Recent year	1	67	2020.2836
Rcd	1	50	2020.34
Liproxstatin	2	69	2019.4203
Deferoxamine	2	82	2019.5122
Ferrostatin	2	216	2019.5741
Erastin	2	266	2019.6128
Depletion	2	225	2019.6356
Lipid reactive oxygen species	2	92	2019.6522
Reduction	2	106	2019.6604
Heme oxygenase	2	61	2019.8033
Ros production	2	75	2019.8133
Cytotoxicity	2	102	2019.8137
Fer	2	103	2019.8155
Oxygen species	2	79	2019.8228
Viability	2	78	2019.8462
Mitochondrial membrane potential	2	51	2019.8627
Inhibition	2	522	2019.8697
Glutathione peroxidase	2	429	2019.8858
Ferroptosis inhibitor	2	164	2019.9268
Glutathione	2	319	2019.9342
Action	2	114	2019.9386
Rsl3	2	72	2019.9444
Ros	2	451	2019.9534
Mouse	2	354	2019.9661
Xct	2	66	2019.9697

Knockdown	2	176	2019.983
Gpx4	2	518	2019.9884
Alpha	2	101	2019.9901
Vivo	2	224	2020
Overexpression	2	124	2020.0081
Concentration	2	160	2020.0125
Mouse model	2	116	2020.0259
Protective effect	2	93	2020.0538
Mu m	2	52	2020.0577
Induced ferroptosis	2	104	2020.0673
Gsh	2	246	2020.0935
Protein expression	2	87	2020.1034
Nrf2	2	158	2020.1329
Upregulation	2	115	2020.1478
Beta	2	79	2020.1519
Day	2	60	2020.1667
Administration	2	103	2020.1748
Downregulation	2	85	2020.2118
Cell viability	2	187	2020.2193
Protein level	2	76	2020.2763
Rat	2	82	2020.2805
Fe_2	2	59	2020.2881
Flow cytometry	2	67	2020.3134
Assay	2	185	2020.3243
Malondialdehyde	2	101	2020.3366
Expression level	2	120	2020.3583
Decrease	2	111	2020.3604
Western blotting	2	57	2020.3684
Mda	2	109	2020.4404
Mir	2	80	2020.5125
Fth1	2	50	2020.56
Hcc	3	75	2020.04
Year	3	70	2020.0429
Hepatocellular carcinoma	3	96	2020.0625
Crucial role	3	60	2020.1
Survival	3	193	2020.114
Model	3	581	2020.1532
Potential role	3	60	2020.1667
Data	3	363	2020.1901
Tumorigenesis	3	67	2020.209
Metastasis	3	89	2020.236
Chemotherapy	3	108	2020.2685
Association	3	92	2020.2717
Identification	3	111	2020.2973
Tumor	3	356	2020.3034
Biomarker	3	136	2020.3309
Relationship	3	178	2020.3539
Poor prognosis	3	60	2020.3667
Analysis	3	509	2020.3713

Gene	3	498	2020.3795
Gene expression	3	73	2020.3973
Group	3	226	2020.4336
Tumor microenvironment	3	92	2020.4457
Progression	3	312	2020.4615
Age	3	69	2020.4783
Patient	3	499	2020.483
Correlation	3	95	2020.5684
Immunotherapy	3	86	2020.6395
Immune cell	3	70	2020.6857
Lncrna	3	50	2020.76
Prognosis	3	217	2020.7742
Database	3	149	2020.8188
Cancer genome atlas	3	92	2020.8478
Signature	3	139	2020.8561
Gene signature	3	73	2020.863
Enrichment analysis	3	91	2020.8681
Overall survival	3	110	2020.8818
Tcga	3	106	2020.8962
Prognostic value	3	68	2020.8971
Roc	3	50	2020.9
Lasso	3	53	2020.9245
Absolute shrinkage	3	56	2020.9286
Prognostic model	3	57	2020.9298
High risk group	3	70	2020.9571
Risk score	3	96	2020.9583
Low risk group	3	78	2020.9615
Nomogram	3	60	2021