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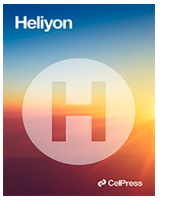

Global research landscape on the crosstalk between ferroptosis and musculoskeletal diseases: A bibliometric and visualized analysis

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ABSTRACT

Over the past 11 years, mounting evidence has suggested a significant association between ferroptosis and the development and progression of musculoskeletal (MSK) diseases, such as osteoporosis and osteoarthritis. However, a comprehensive bibliometric analysis summarizing the relationship between ferroptosis and MSK diseases is currently lacking. The present study collected articles and reviews on the topic of ferroptosis in MSK diseases. The data were collected from January 1st, 2012 to June 30th, 2023 by screening the Web of Science database. Various tools, including VOSviewer, CiteSpace, Pajek, the R package, and others, were used to conduct bibliometric and visualization analyses. Notably, China, the USA, and Italy emerged as primary contributors, jointly accounting for over 80 % of published documents, thereby shaping research in this domain. Among the diverse institutions, Shanghai Jiao Tong University, Soochow University, and Huazhong University of Science and Technology displayed the highest productivity levels. The most prolific authors include Sun Kai, Shang Peng, and Jing Xingzhi. *Oxidative Medicine and Cellular Longevity* stood out with the largest number of publications in this area. The five most significant disorders in this field are bone fractures, osteosarcoma, bone neoplasms, joint diseases, and osteoporotic fractures. This study represents an inaugural comprehensive bibliometric analysis, presenting a holistic view of the knowledge framework and developmental patterns in ferroptosis concerning MSK diseases over the previous eleven years. This information can aid researchers in acquiring a thorough grasp of this domain and offer invaluable insights for forthcoming explorations.

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1. Introduction

The global prevalence of musculoskeletal (MSK) diseases, such as osteoporosis (OP), osteoarthritis (OA), and osteosarcoma (OS), has significantly increased due to the extension of human life expectancy and the aging of the population [1]. These diseases have now become significant public health concerns [2–4], as they not only are the most common causes of disability but also impose a substantial burden upon public health and social care systems [5]. This situation is particularly challenging in developing nations due to the global economic downturn and increased uncertainty. Therefore, gaining an in-depth understanding of the mechanisms underlying these diseases is pivotal for developing tailored interventions.

Ferroptosis, a novel iron-dependent mode of cell death, is distinguished by the accumulation of lipid peroxides and reactive oxygen species [6]. Since its discovery in 2012, ferroptosis has gained prominence in research and has garnered increasing attention from investigators in various fields, including carcinoma, cardiovascular diseases, and neurodegenerative diseases [7]. As scientific exploration progresses, mounting evidence indicates that ferroptosis occupies a prominent position in both the development and advancement of MSK disorders [8]. Both impaired iron homeostasis and redox imbalance play a significant role in the onset, progression, and therapeutic management of MSK diseases, such as OA, OP, and OS [9,10]. Thus, focusing on ferroptosis could offer a promising avenue for preventing and treating MSK disorders.

Despite the existence of numerous reviews focusing on the role of ferroptosis in MSK diseases [7–9,11–13], there remains a dearth of visual analyses and comprehensive summarizations pertaining to progression trends, key authors, and research focal points. Hence, the primary objective of this investigation was to conduct a bibliometric and visual analysis of ferroptosis in the context of MSK diseases over the past eleven years. This investigation serves as a valuable resource for both seasoned professionals and newcomers, enabling them to conduct thorough assessments within their respective fields, discover new realms of interest, and formulate well-informed strategies for future research, all facilitated through a visual approach. This significantly enhances the efficiency and effectiveness of researchers. To the best of our knowledge, no prior bibliometric investigations have been undertaken regarding this specific subject matter.

2. Materials and methods

2.1. Data collection and search methodology

The Web of Science Core Collection (WoSCC) (https://www.webofscience.com/wos/) is commonly employed for conducting bibliometric analyses to track the evolution of scientific subjects. Recognized for its capacity to provide standardized and high-quality academic publication data [14], this study engaged in a thorough online exploration within the WoSCC database. The primary focus was on research articles and reviews concerning ferroptosis within the context of MSK diseases. The search scope encompassed publications spanning January 1st, 2012, to June 30th, 2023. The retrieval approach incorporated Medical Subject Heading terms and unrestricted keywords. To ensure the search strategy's sensitivity and precision, it underwent multiple rounds of testing and refinement by three authors (SYC, YHW, and YHY). A comprehensive outline of the search methodology is provided in the Supplementary Materials.

2.2. Eligibility criteria

The study employed well-defined inclusion and exclusion criteria. The inclusion criteria encompassed studies pertinent to ferroptosis in the context of MSK diseases, which included original research articles and reviews published in English-language literature. Conversely, dissertations, letters, commentaries, editorials, conference abstracts, and studies published under similar or distinct titles in different journals were excluded. Any discrepancies that emerged were addressed through discussion and resolved through adjudication by a third researcher (YHY). If consensus could not be achieved, an experienced orthopaedist (HZ) made a final decision.

2.3. Statistical analysis and visualization

The entire dataset was acquired from WoSCC and imported into Microsoft Excel Office 2021 (Microsoft Corporation, Redmond, USA), VOSviewer 1.6.18 (Leiden University, Netherlands), CiteSpace version 6.1.6 (Chaomei Chen, China), Pajek version 5.16 (University of Ljubljana, Slovenia), and the chorddiag and Clusterprofiler R package (R Studio, version 4.2.0).

VOSviewer and Pajek were employed for co-occurrence analysis, facilitating the identification of co-occurrence patterns among countries, institutions, authors, journals, research fields, keywords, and diseases. The Scimago Graphica tool was utilized to examine the temporal evolution of keyword intensity. CiteSpace was applied for visual analysis, enabling the generation of pertinent visual maps for countries, institutions, authors, journals, co-cited literatures, and keywords. Furthermore, the chorddiag R package was utilized for visual analysis of the publishing landscape. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted using the clusterProfiler R package.

3. Results

3.1. Yearly volume and tendency

The process of data retrieval and collection is outlined in Fig. 1A. A study's volume of publications during a specific period signifies its research trend [15]. From 2012 to 2023, a comprehensive compilation of 523 relevant pieces of literature (comprising 394 original articles and 129 reviews) related to ferroptotic research in MSK diseases was amassed, resulting in an average annual publication count of 43.58. Over the last eleven years, there has been a consistent upward trajectory in the volume of scholarly output within this particular field. Starting in 2021, the yearly count of pertinent scholarly publications exceeded 50, reaching a peak of 167 in 2022. This figure represents an increase of over 15 times compared to the count documented in 2012, with an annual growth rate of 36.48 %. This phenomenon indicates a sustained surge in research activity, highlighting the substantial research significance of this domain. To demonstrate the yearly distribution pattern more comprehensively, an exponential equation, $y = 6.1692e^{0.2378x}$ ($R^2 = 0.8994$, where x represents the year and y indicates the annual publication quantity), was adopted, resulting in a good-fitting curve (Fig. 1B). According to this curve, the number of annual investigations is anticipated to steadily rise, indicative of the growing interest in ferroptosis within MSK diseases. Therefore, it is reasonable to infer that this domain will witness a period of significant advancement in the upcoming years.

3.2. Research countries/regions and their nexus

Research pertaining to ferroptosis in MSK diseases has been undertaken across 45 countries/regions. By establishing a minimum

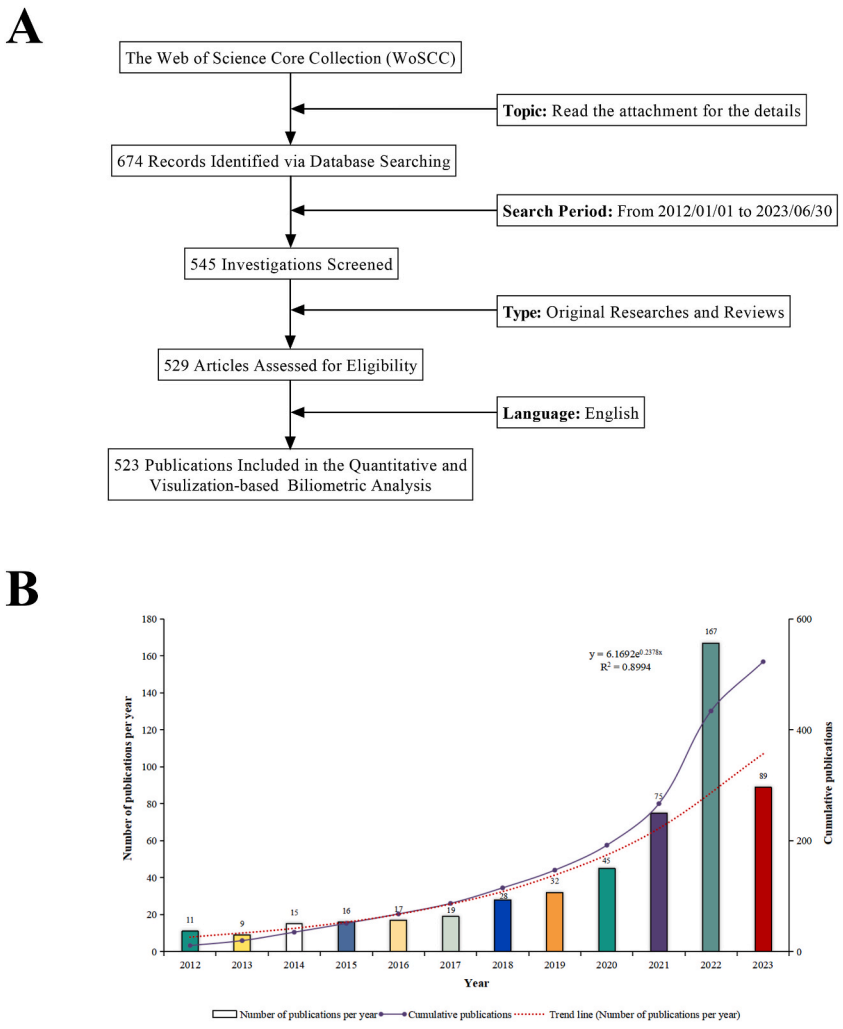


Fig. 1. (A) Flow diagram of the literature search and selection. (B) Research publications on "ferroptosis-musculoskeletal diseases" (increasing trend) from 2012 to 2023.

publication count of three from each country/region, we generated national collaboration diagrams for the study of ferroptosis within MSK diseases (Fig. 2A and B). Within the geographical representation, individual spheres denote distinct nations or regions, with each sphere's color indicating the clustering relationship among the study areas. These study areas are grouped based on the extent of mutual collaboration, resulting in the formation of four distinct clusters. The thickness of the connecting line between the spheres indicates the extent of collaboration between countries, while the dimensions of the spheres are directly associated with the number of published documents per nation. The chord diagram portrays distinct countries or regions by representing their peripheral curve segments. The length of each segment signifies the quantity of publications originating from that specific location. Furthermore, the thickness of connections between countries is directly proportional to the intensity of collaboration.

Observing the global productivity map depicted in Fig. 2A, it is evident that the majority of papers were predominantly published in Asian, North American, and European countries. China leads with the highest number of published documents, contributing 341 publications, which constitutes 65.20 % of the overall total. This is followed by the USA and Italy, contributing 9.75 % (n = 51) and 6.12 % (n = 32), respectively. Naturally, this distribution is closely linked to the economic development levels of the mentioned countries and their respective emphasis on scientific research. The frequency of academic collaboration between China and the USA surpasses that of any other pair of countries (link strength = 19) (Fig. 2B). Similarly, the number of publications can serve as a reflection of a country or region's stature within this field [16]. Both China and the USA boast the highest number of publications in the ferroptosis field related to MSK diseases, indicating their elevated academic status and influence. The strong collaboration between these two nations is poised to drive theoretical innovation and address existing technical challenges in this domain [17].

Citation bursts play a crucial role in identifying items that have undergone significant citation increases within a specific timeframe. They provide insights into the dynamics and trajectory of a research field. Analyzing items that have rapidly accumulated citations assists in recognizing emerging trends within a specific research domain that has garnered attention from researchers. The citation bursts for the top 10 countries are presented in Fig. 2C. The red line depicted on the graph represents the magnitude of the citation bursts for each of the prominent countries. During the period from 2014 to 2019, Italy experienced a notable surge in publications (strength = 5.76), closely followed by the USA (strength = 4.96).

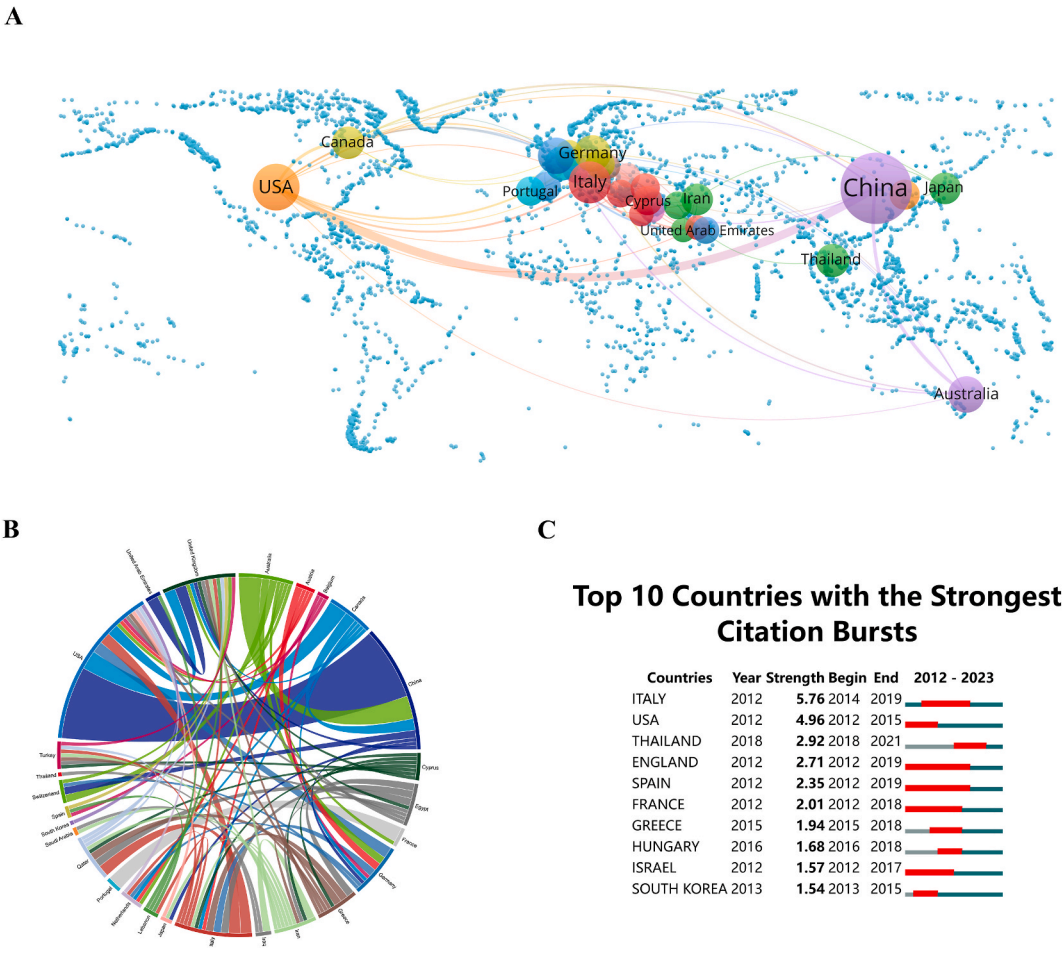


Fig. 2. (A) Co-occurrence network and cooperation geo-heatmap. (B) Chord maps for country/region partnerships. (C) "Ferroptosis-musculoskeletal diseases" research document numbers are highlighted in the top 10 countries (red areas represent surges in documents).

3.3. Insights into institutional performance

Over the past eleven years, a cumulative total of 757 establishments have embarked on investigations related to ferroptosis in the context of MSK diseases. Notably, both Shanghai Jiao Tong University and Soochow University emerged as the most prolific institutions (n = 25, 4.78 %), followed closely by Huazhong University of Science and Technology (n = 24, 4.58 %). The cooperation relationship maps and clustering maps of the research institutions were generated by applying a minimum publication threshold of six and two documents per institution, respectively (Fig. 3A and B). Different color regions correspond to distinct clustering information. The level of collaboration intensity among the institutions is symbolized by the thickness of connections between circles, while the size of the circle is positively correlated with the quantity of documents published by the respective organization.

Regarding interinstitutional collaboration, our observations revealed that Shanghai Jiao Tong University displayed remarkable enthusiasm in engaging with partnering institutions. The institutions with notable citation bursts were identified through CiteSpace (Fig. 3C), with the highest-ranked item being Soochow University's burst from 2012 to 2016. However, it is regrettable that this trend has not been consistently maintained over the past seven years. Additionally, Wuhan University and Sichuan University were identified as starting citation bursts in 2021, which continued until 2023.

3.4. Analysis of authors

After scrutinizing authorship data, a comprehensive count of 3185 authors was identified as contributors to publications related to ferroptosis in MSK diseases. Among this group, 35 authors boasted a publication record of at least five papers. Utilizing the VOSviewer software, we generated co-authorship overlay visualization maps, setting a minimum requirement of four documents per author. The graphical representation employs circles whose sizes are in direct proportion to the count of documents that each individual has authored. Additionally, distinct clusters are discerned through the utilization of varied colors. The level of collaboration is indicated by the thickness of lines that connect the circles. A total of 68 acknowledged authors met the established threshold. Among them, Yao Xue and Zhang Yan displayed the most closely-knit collaborative relationships (Fig. 4A). Additionally, Sun Kai, Shang Peng and Jing Xingzhi emerged as the top three contributing authors, accentuating their notable contributions to the field of "ferroptosis-MSK

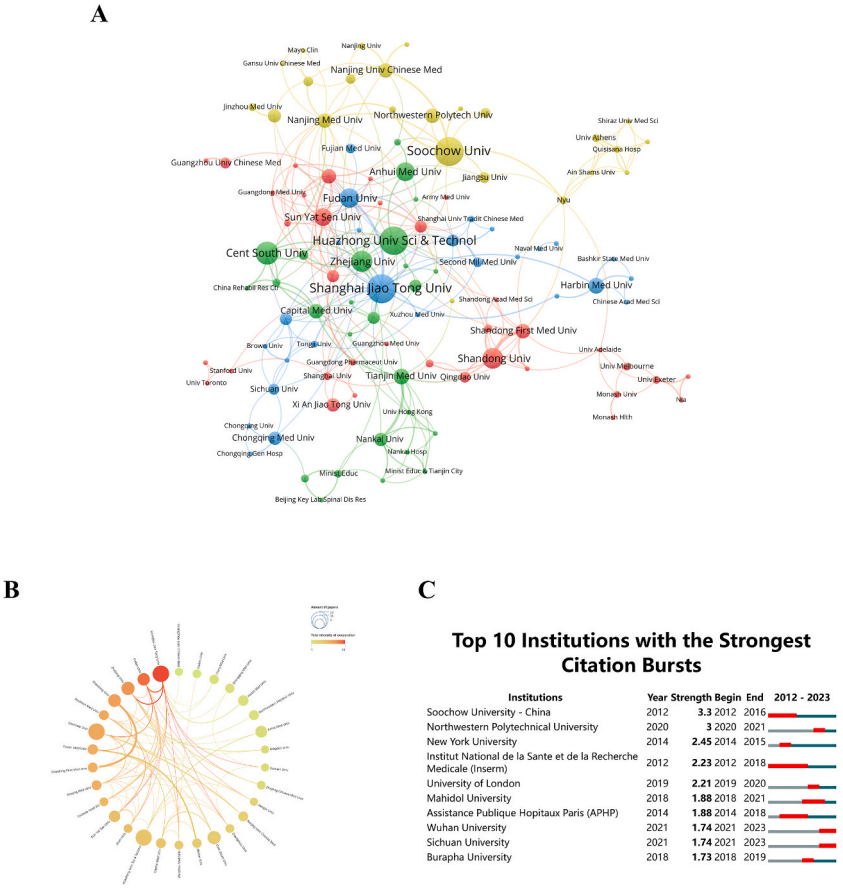
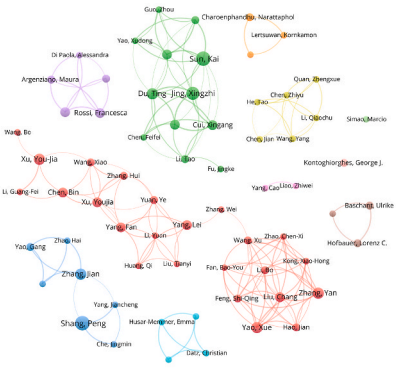
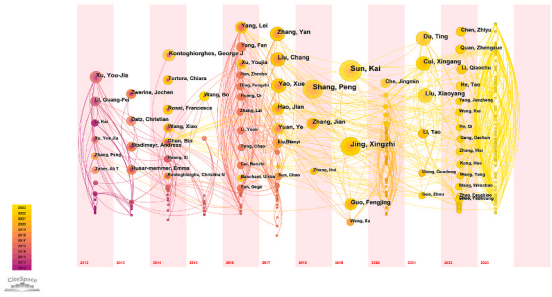


Fig. 3. (A) Clustering networks of relevant research institutions. (B) Diagram of institutional cooperation intensity. (C) Citation bursts at the top 10 institutions (red bars represent burst periods for institutions).

A



B



C

Top 10 Authors with the Strongest Citation Bursts

Authors	Year	Strength	Begin	End	2012 - 2023
Xu, You-Jia	2012	**2.68**	2012	2016	
Li, Guang-Fei	2012	**2.3**	2012	2015	
Du, Ting	2019	**2.29**	2021	2023	
Yang, Fan	2016	**2**	2016	2018	
Li, Kai	2012	**1.94**	2012	2013	
Huang, Xi	2014	**1.87**	2014	2015	
Liu, Xiaoyang	2021	**1.86**	2021	2023	
Cui, Xingang	2021	**1.86**	2021	2023	
Feng, Chao	2016	**1.81**	2016	2017	
Cai, Benzhi	2016	**1.81**	2016	2017	

Fig. 4. (A) Network of collaboration between authors. (B) Temporal overlay of the author's cooperative network. (C) Top 10 authors with the strongest citation bursts in publications related to "ferroptosis-musculoskeletal diseases".

diseases".

Simultaneously, a distinct analysis was conducted on nodes situated within the identical temporal region. In the graphical depiction, each sphere corresponds to an author, with its magnitude directly proportional to the extent of their published works. The depicted time zone correlates to the year of an author's initial publication. Purple indicates an author's early publications, while yellow signifies recent ones. Additionally, the presence of overlaid colors indicates publications in the respective year. When numerous overlaid colors are present, they form an annual wheel, symbolizing an author's productive and continuous publication pattern (Fig. 4B). The top three authors, Sun Kai, Shang Peng and Jing Xingzhi, exhibit a higher level of productivity and a sustained history of publishing their work.

Citation bursts serve as a significant metric, indicating an author's citation frequency within a specific field over a given time frame. Fig. 4C presents the top 10 authors who have accumulated the most citations related to ferroptosis in MSK diseases. Leading the list is Xu Youjia with a citation burstness strength of 2.68, closely followed by Li Guangfei. Notably, authors Du Ting, Liu Xiaoyang, and Cui Xingang have observed a remarkable upsurge in their publication output over the past three years, suggesting their discernible inclination toward research in this specific field. These highly cited authors can provide essential inspiration to the "ferroptosis-MSK diseases" field and, to a certain extent, serve as research benchmarks, guiding future research directions.

3.5. Analysis of journals and related fields

Through a visualization of journal publication data, 268 journals have featured articles on ferroptosis in MSK diseases. By setting a minimum threshold of two documents published by each journal, a thermodynamic chart was generated to illustrate the distribution of

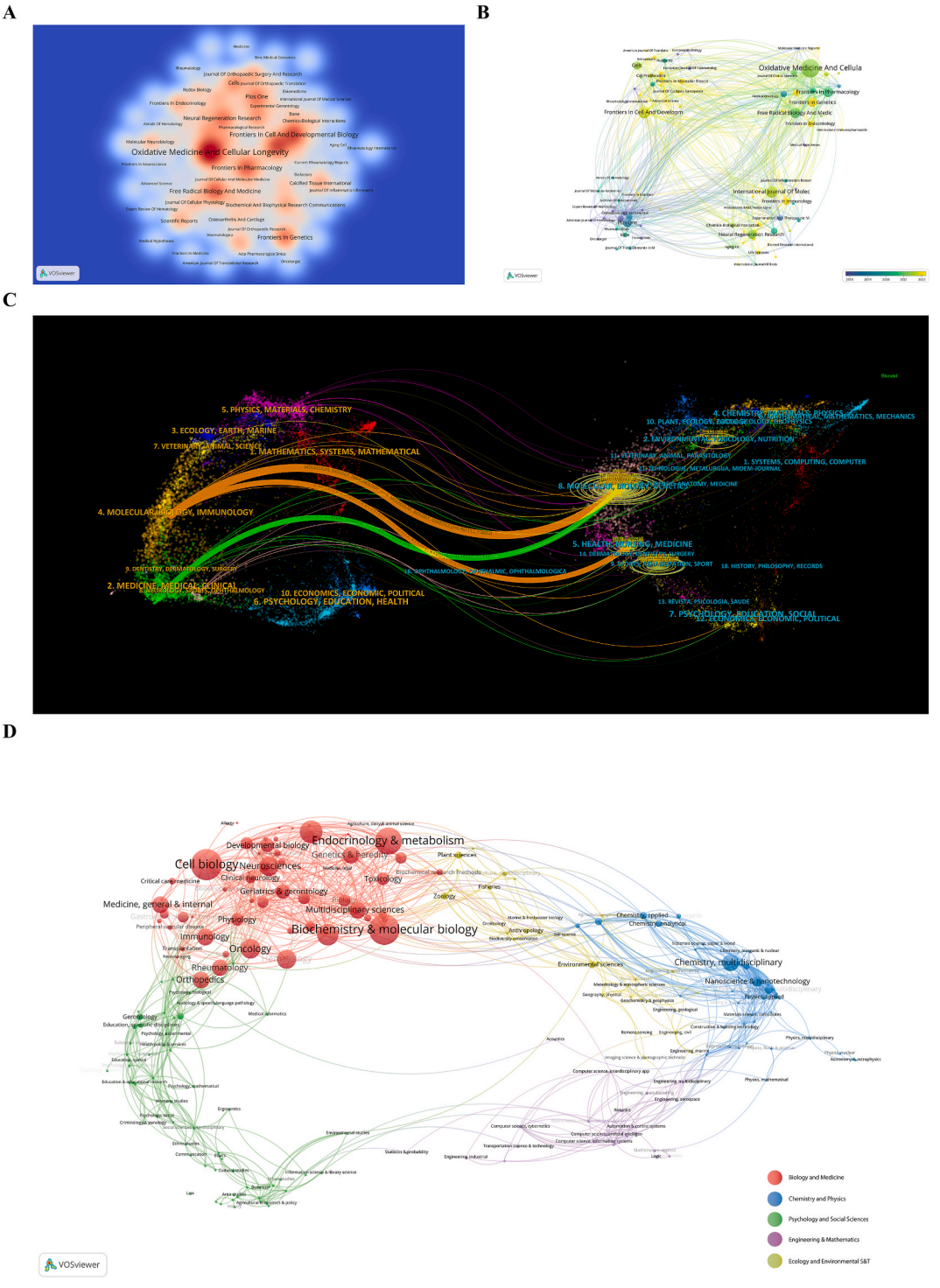


Fig. 5. (A) Density visualization map of journal citations. (B) Journal distribution based on average publication year (blue: earlier, yellow: later). (C) A dual-map overlay of journals related to ferroptosis in musculoskeletal diseases. (D) Analyses of research subject areas.

documents across these journals. The quantity of published journal documents shows a positive correlation with color intensity (Fig. 5A). The journal "*Oxidative Medicine and Cellular Longevity*" stands out with the highest number of issued documents (n = 23). It is closely followed by "*Frontiers in Cell and Developmental Biology*" (n = 13) and the "*International Journal of Molecular Sciences*" (n = 13). Journals are color-coded based on their mean year of establishment (Fig. 5B). The sizes of the circles and labels correspond to the frequency of occurrence, while the color of the circle reflects the mean publication year. It is evident that journals such as *Advanced Science* and *International Immunopharmacology* are emerging within this specific field, signified by their representation in yellow.

The dual-map overlay of journals effectively reflects the interdisciplinary distribution of journals, the evolution of citation trajectories, and the shift of scientific research centers [18]. The map labels illustrate the diverse study areas encompassed by all the journals. Journals that cite others are positioned on the left side of the map, while the journals being cited are located on the right side.

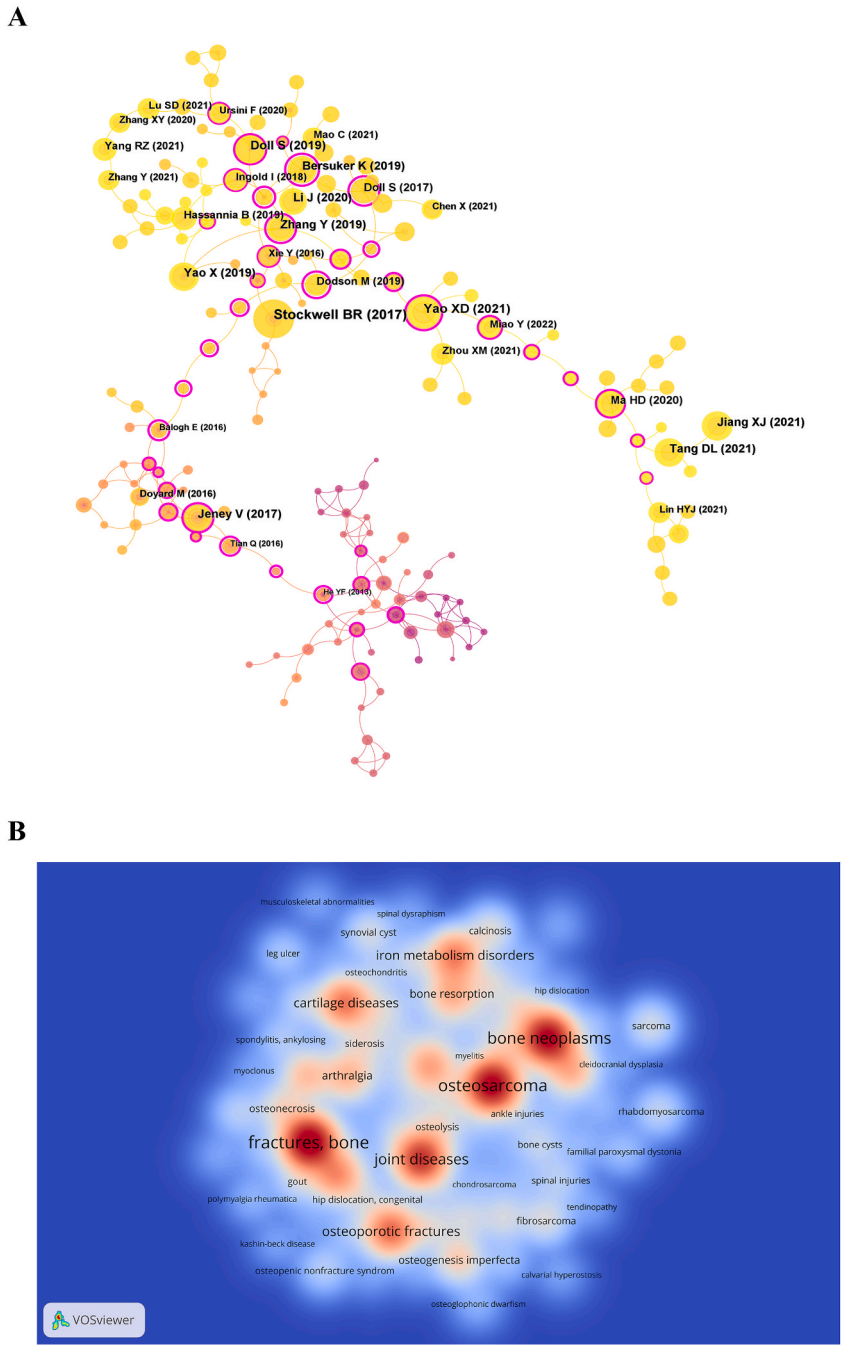


Fig. 6. (A) Diagram of co-cited references. (B) Density visualization map of related diseases.

The reference paths are visually depicted by distinct colored lines, originating from the citation map and concluding there. The width of these connecting pathways correlates strongly with the frequency of z-score-scaled citations [14]. Research related to "ferroptosis-MSK diseases" was associated with five primary categories, namely molecular biology, immunology, genetics, and clinical medicine, as displayed in Fig. 5C.

VOSviewer software facilitated a visual analysis of the domain categories of 523 articles, leading to the clustering of these articles into five major fields. Fig. 5D presents this clustering, with spheres of differing colors denoting distinct domains. The results reveal that the bulk of the related research is centered in the field of "Biology and Medicine", with a notable proportion of articles falling within the subdivisions of "Cell Biology" and "Biochemistry and Molecular Biology".

3.6. Co-cited references and related diseases

One of the objectives of this section was to identify seminal papers within this domain and trace evolving themes over time through an analysis of co-cited references. Research papers with a significant number of co-citations are often regarded as fundamental to a specific field of study, as they provide essential contextual knowledge and reflect the research objectives of the community of foundational researchers. The review titled "Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease" [19], published in *Cell* by Brent Stockwell et al., in 2017, garnered the most citations (n = 74), closely followed by an original research paper named "Chondrocyte Ferroptosis Contributes to the Progression of Osteoarthritis" [20], published in the *Journal of Orthopaedic Translation* by Xudong Yao et al., in 2021 (Fig. 6A). Subsequently, employing a minimum threshold of two occurrences per disease and utilizing VOSviewer software, a thermodynamic diagram was generated to visually depict the data (Fig. 6B). A positive correlation is observed between color intensity and disease frequency. The top five disorders identified were bone fractures, OS, bone neoplasms, joint diseases, and osteoporotic fractures.

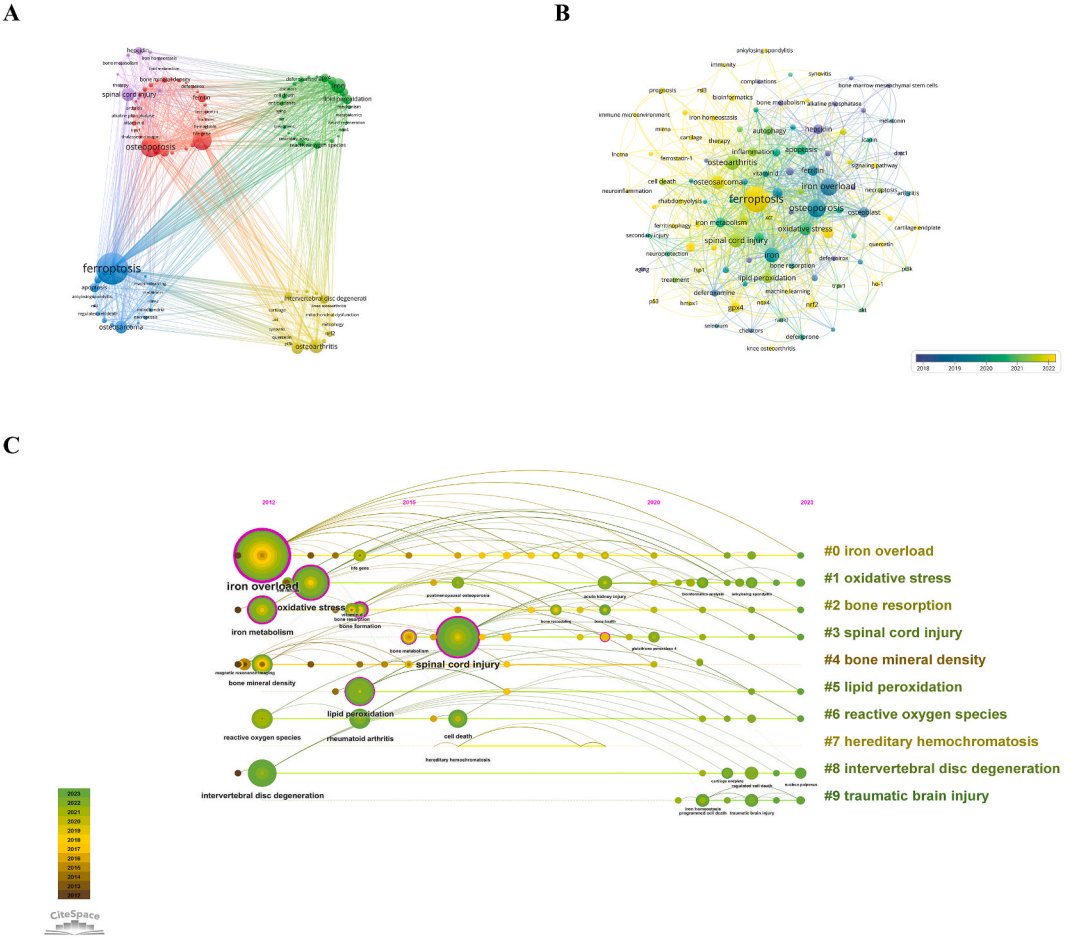


Fig. 7. (A) Visualization of keywords clustering. (B) Keywords intensity visualization timing overlay. (C) Co-occurrence of temporal trends in keywords.

3.7. Keywords

Keywords play a pivotal role in scholarly papers, as they reflect the existing knowledge foundation and provide guidance on the trajectory and developments within a relevant academic domain. Utilizing co-occurrence cluster analysis of keywords, we generated a visual map (Fig. 7A). Nodes, represented as circles with labels, were employed. The size of the circles is positively correlated with the frequency of the corresponding keywords. Moreover, the thickness of the lines connecting the circles demonstrated a positive association with the intensity of the relationships among the keywords. To categorize the nodes, distinct clusters were formed based on their color, where each color signified a unique research direction. A total of five clusters were successfully identified. To provide a visual representation of the average year of emergence for different keywords, Fig. 7B exhibits colors indicating specific time periods. Keywords introduced during the initial investigation stage are shown in blue, while more recent ones are highlighted in yellow.

An examination of the temporal progression of keywords associated with “ferroptosis-MSK diseases” through clustering and

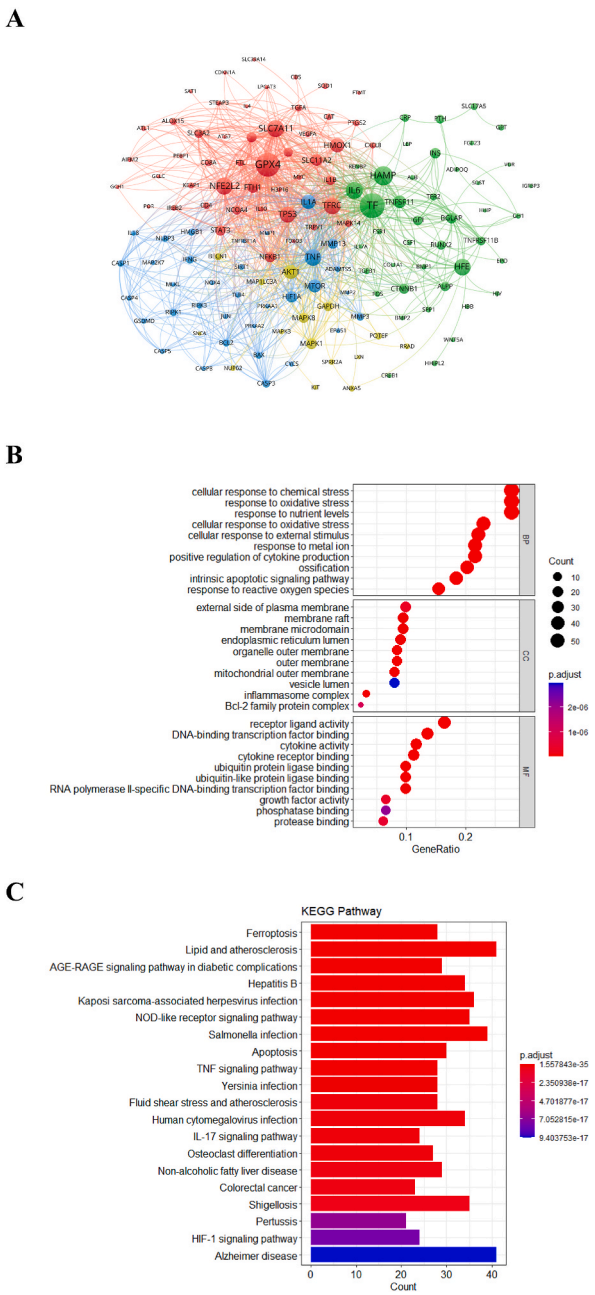


Fig. 8. (A) VOSviewer Critical Gene Clustering Visualization. (B) Bubble plots of GO enrichment analysis. (C) KEGG pathway enrichment analysis.

timeline analysis reveals that the color purple signifies keywords that appear in earlier stages, while yellow denotes recently emerged keywords. Additionally, the presence of superimposed colors indicates the occurrence of keywords in specific years. Notably, red nodes represent pivotal points, and keywords within the same cluster are positioned along a shared horizontal line. Furthermore, the proximity of keywords to the top of the visual representation corresponds to their increasing chronological placement toward the right side. This figure facilitates determining the quantity of keywords within each cluster, where a higher number of keywords indicates greater significance within the field of clustering. Additionally, the temporal duration of keywords within each category can be observed. As depicted in Fig. 7C, the keywords were organized into ten clusters: iron overload (#0), oxidative stress (#1), bone resorption (#2), spinal cord injury (#3), bone mineral density (#4), lipid peroxidation (#5), reactive oxygen species (#6), hereditary hemochromatosis (#7), intervertebral disc degeneration (#8), and traumatic brain injury (#9). Clusters #0, #1, #2, #3, #5, #6, #8, and #9 consistently advance within the realm of "ferroptosis-MSK diseases" research.

3.8. Key genes and pathways

The analysis of critical genes and pathways assists new researchers in swiftly comprehending significant gene targets and pathways associated with "ferroptosis-MSK diseases". A visual map (Fig. 8A) was generated through the implementation of a co-occurrence cluster analysis on genes associated with "ferroptosis-MSK diseases". The map exclusively portrayed relevant genes that exhibited a minimum of six occurrences. Nodes are represented by circles and labels, with the size of the circles indicating the frequency of gene occurrence. The strength of the relationship between genes is reflected in the thickness of the circle lines. Nodes of varying colors form distinct clusters, with each color representing gene clusters in different domains.

Moreover, GO and KEGG enrichment analyses were conducted on genes associated with "ferroptosis-MSK diseases", with a focus on the 215 genes that appeared more than four times in the article (Fig. 8B and C). In the GO enrichment analysis bubble chart, each bubble corresponds to a GO term. The bubble size mirrors the number of genes within that function, while the color indicates the extent of enrichment. On the X-axis, the GeneRatio value is represented, denoting the proportion of genes linked to the GO term within the background gene set relative to the total gene count. A larger GeneRatio value on the X-axis signifies a greater number of genes associated with the GO term and potentially higher significance. The Y-axis signifies the terminology or categorization of GO terms, where each node corresponds to a distinct biological process, molecular function, or cellular component.

The GO functional enrichment findings are presented in Fig. 8B, encompassing biological processes (BP), molecular functions (MF), and cellular components (CC). Concerning BP, the genes exhibit enrichment in functions such as cellular response to chemical stress, response to oxidative stress, and response to nutrient levels. For CC, the genes demonstrate enrichment in functions such as the external side of the plasma membrane, membrane raft, and membrane microdomain. Regarding MF, the genes exhibited enrichment in functions such as receptor-ligand activity, DNA-binding transcription factor binding, and cytokine activity.

KEGG pathway enrichment analysis was executed to discern the top 20 signaling pathways, yielding a histogram. On the X-axis, the count of genes significantly enriched in each pathway is depicted, while the Y-axis represents distinct signaling pathways. The height of each histogram column indicates the gene count within it and its significance following enrichment. Fig. 8C depicts that this subject is mainly linked to signaling pathways such as lipid and atherosclerosis, ferroptosis, and the AGE-RAGE signaling pathway in diabetic contexts.

4. Discussion

The escalating rise in the global elderly population has made aging the primary determinant for MSK disorders, like OA, OP, and lumbar disc herniation. If not handled effectively, these disorders can result in unfavorable consequences. Gaining a profound understanding of the fundamental mechanisms behind MSK diseases and formulating precise intervention approaches holds immense clinical importance. The emergence of ferroptosis as a novel form of programmed cell death (PCD) has rendered it a pivotal focal point within the realm of cell death research, gaining prominence since its conception in 2012. Notably, ferroptosis occupies a significant place in modulating bone homeostasis and regeneration and mirrors promising remedial vistas [12]. The interplay between ferroptosis and MSK diseases has undergone initial scrutiny by scholars subsequent to the early documentation of ferroptosis. Subsequently, the annual volume of publications within the arena of ferroptosis in MSK diseases has exhibited a progressive increase, signifying an escalating scholarly interest in this domain. Focusing on ferroptosis may endow opportunity for targeting ferroptosis to treat MSK diseases. The forthcoming years may witness an upsurge in publications within this field.

The quantity of pertinent research articles originating from a specific country or region can, to some extent, mirror the significance of scientific research endeavors, economic capacity, and the level of scientific research within said location. As the world's two largest economies, China and the USA also exhibit the highest degree of willingness and collaboration intensity. The combined publication count from these two nations constitutes 74.95 % of the global total, solidifying their preeminent contributions to the field. For instance, the aforementioned two countries have authored quite a number of high-quality articles focusing on redox biology [19], potential regulatory mechanisms, signaling pathways [21], and interplay with other forms of PCD [22,23].

International cooperation has made significant contributions to the rapid development of the field of "ferroptosis-MSK diseases" in four major ways. Firstly, it promotes academic complementarity. Different countries, such as China and the USA, possess unique expertise and advantages in various subsectors. By collaborating internationally, resources can be shared and multilateral benefits can be achieved. For instance, one country may have made notable breakthroughs in a specific scientific field, while another country excels in basic research and technological applications. Through multilateral cooperation, knowledge exchange and technology transfer can be accomplished. Secondly, international cooperation fosters joint research interests. Countries with shared research interests and

goals in specific fields or issues can strengthen each other's research capabilities and outputs through collaboration. This collaboration may involve cross-border scientific teams, joint research projects, or co-authored publications. Thirdly, international cooperation provides funding and facility support. Partners from different countries often have complementary relationships in terms of funding and facilities. While one party may provide financial support, the other party may contribute laboratory equipment or research facilities, facilitating the smooth progress of "ferroptosis-MSK diseases" research projects. Last but not least, international cooperation enhances the international reputation of participating countries. By engaging in academic cooperation with other nations, countries can elevate their standing and reputation within the international academic community. International cooperation often brings forth additional opportunities for collaboration, resources, and influence.

Based on the cluster analysis presented in Fig. 3A and the relationship analysis depicted in Fig. 3B, it becomes evident that the foremost ten institutions excelling in the realm of "ferroptosis in MSK diseases" all hail from China. The publication highlight chart (Fig. 3C) similarly underscores the prevalence of Chinese institutions. These data collectively underscore China's global preeminence in terms of aggregate publication count and publication velocity. Notably, the majority of institutions showed a preference for domestic collaboration over international collaboration. This phenomenon can be ascribed to the collaboration patterns prevalent in China, which exhibit a preference for domestic institutions rather than participating in broader international cooperation. To promote a broader worldwide exchange of ideas, resources, and expertise, it is essential to prioritize future collaborations between Chinese institutions and their international counterparts. Therefore, it is imperative to comprehend the research institution landscape and its collaborative tendencies to propel the field of "ferroptosis-MSK diseases" forward. Fostering innovation and ultimately enhancing human well-being will be indispensable in promoting enduring research endeavors, cultivating international partnerships, and harnessing the capabilities of prominent institutions.

Regarding journals displaying a substantial publication output, the preeminent trio comprises *Oxidative Medicine and Cellular Longevity*, *Frontiers in Cell and Developmental Biology*, and *International Journal of Molecular Sciences*. It is of significance to highlight that *Oxidative Medicine and Cellular Longevity*, a reputable journal within the oxidative stress domain, was removed from the Science Citation Index of the WoSCC database due to peer review integrity concerns. Consequently, exercising caution is essential when perusing research reports within the "ferroptosis-MSK diseases" field that are published in *Oxidative Medicine and Cellular Longevity*.

Based on the co-citation analysis chart (Fig. 6A), it becomes evident that Brent Stockwell's work in 2017 accumulates the highest number of co-citations within this study. As a pioneer in the field of ferroptosis, Brent Stockwell's contributions command substantial esteem within the international academic community. For over a decade, he has been at the forefront of advancing the field of ferroptosis. He has been a source of inspiration for subsequent scholarly investigations due to his continuous publication of findings and noteworthy research achievements in the initial phases of this field of study. This underscores the significance of the ongoing contributions made by eminent researchers in sustaining the progress and vitality of the field.

Disease-related genes constitute the core elements of this research subject, effectively serving as dual indicators: one for identifying changing research trends, and the other for detecting shifts in research direction and the deepening of investigations. As demonstrated in Fig. 8A, the five genes with the highest frequency were TF, GPx4, HAMP, SLC7A11, and NFE2L2. Under normal homeostasis conditions, iron primarily binds to transferrin (TF) in systemic iron reservoirs, subsequently contributing to erythropoiesis. Macrophages engulf senescent erythrocytes, releasing iron from these cells into the systemic iron pool via ferroportin (FPN), a process commonly referred to as iron recycling [12]. Hepcidin, encoded by the hepcidin antimicrobial peptide (HAMP) gene, plays a crucial role as a hormone secreted by the liver to regulate iron homeostasis. When hepcidin binds to FPN, it induces the degradation of FPN, impairing its ability to excrete iron ions. Consequently, the absorption of iron by duodenal epithelial cells and the recycling of iron by macrophages are inhibited. Any inhibition of HAMP expression or dysregulation of FPN function can result in abnormal iron efflux, leading to disorders of iron metabolism in the body [24]. Meanwhile, the sensitivity of ferroptosis is directly linked to the level of expression of nuclear factor erythroid 2 like 2 (Nrf2), also known as nuclear factor erythroid 2-related factor 2 (NFE2L2). When the expression of Nrf2 increases, it inhibits ferroptosis, whereas a decrease in expression promotes ferroptosis [25,26]. The mechanisms by which Nrf2 regulates ferroptosis involve two primary aspects. First, Nrf2 enhances the antioxidant system by upregulating the expression of glutathione (GSH) and glutathione peroxidase 4 (GPx4), thereby improving antioxidant functionality. Second, Nrf2 promotes the expression of ferritin and FPN, contributing to the storage or export of free iron. Consequently, this reduction in iron accumulation prevents ferroptosis [27]. Solute carrier family 7 member 11 (SLC7A11), it acts as a cystine/glutamate antiporter that plays a pivotal role in importing cystine for GSH biosynthesis and antioxidant defense [28].

Correspondingly, targeting the aforementioned key genes to regulate ferroptosis could potentially provide a novel approach for preventing and treating MSK diseases. For malignant orthopaedic tumors, such as OS, ferroptosis activators that target the mentioned genes are considered viable options. These primarily include, but are not limited to, iron metabolism-related activators (e.g., ferric ammonium citrate [29], artesunate [30], dihydroartemisinin [31]), iron-containing nanoparticles [32–35], Nrf2 antagonists (trigonelline [36], brusatol [37]), regulators of Nrf2-related pathways (e.g., BAY 11–7085 [38]), inhibitors of the cystine-glutamate antiporter (System Xc^-) (e.g., sulfasalazine [39], sorafenib [39]), and GPx4 inhibitors (e.g., ras-selective-lethal compound 3 [6]). For numerous age-related orthopaedic degenerative diseases such as OA and OP, ferroptosis inhibitors present a promising avenue for future drug research. These drugs encompass a range of options, including iron ion chelating agents (e.g., deferoxamine [40], deferiprone [41], deferasirox [42], dexrazoxane [43]), GPx4 activators (e.g., dopamine [44], carvacrol [45], selenium [46]), and ferroptosis inhibitors that target System Xc^- (e.g., *N*-acetylcysteine [47], GSH [48]).

For signaling pathways, Fig. 8C depicts that this subject is mainly linked to signaling pathways such as lipid and atherosclerosis, ferroptosis, and the AGE-RAGE signaling pathway in diabetic contexts. It is noteworthy that numerous MSK diseases, such as OA, OP, and lumbar disc herniation, are also types of the age-correlated disorders that are commonly seen in middle-aged and elderly adults. These patients also tend to suffer from other chronic diseases, such as diabetes mellitus and cardiovascular and cerebrovascular

diseases (atherosclerosis). From this, further investigation is required to explore the interplay between ferroptosis and above-mentioned signaling pathways in the context of a rapidly aging world population, with a view to identify potential targets for synergistic combination therapy.

Unlike previous studies that solely relied on meta-analysis or narrative reviews, the incorporation of bibliometric tools in this analysis provides a more lucid representation of evidence pertaining to research focal points and trends across diverse dimensions [49]. This is the first bibliometric study to map and characterize the knowledge landscapes on "ferroptosis-MSK diseases" over the past eleven years, thereby serving as a comprehensive and unbiased reference for future advancement, while certain limitations are inevitable.

This study has some limitations. 1) Due to the inherent limitations of the software CiteSpace, the publications included in this study were exclusively extracted from WoSCC, thereby resulting in an inevitable presence of selection bias. 2) The citation count of a paper is subject to the influence of multiple confounding factors, such as publication time, research area, journal, and authorship. Consequently, the citation count may not provide an accurate measure of a paper's impact. 3) Due to the large number of papers, it was not possible to comprehensively read every paper and conduct an in-depth analysis of the subfields, so it was necessary to give equal weight to high-quality and low-quality publications and literature, which may damage the credibility of this study. 4) Bibliometric techniques rely on natural language processing, a process that has been found to potentially exhibit bias, as indicated by previous bibliometric investigations [49–51]. 5) The inclusion of solely English documents may have introduced a potential publication bias. 6) Ultimately, in the process of literature retrieval, the newly published literature and some key words may not be retrieved and included in the statistical analysis, and the results may be affected by incomplete literature collection.

5. Conclusion and perspectives

The present study utilizes bibliometric analysis to investigate the field of ferroptosis in relation to MSK diseases. The analysis focuses on international collaboration, publication trends, and research hotspots. These findings enable the scientific community to identify emerging ideas and frontiers that will shape future ferroptosis research for MSK diseases. Keeping up with these trends and utilizing existing knowledge to propel progress in this field is of utmost importance for researchers. However, numerous pressing issues remain concerning "ferroptosis-MSK diseases", including but not limited to the following: (1) the primary factor responsible for triggering ferroptosis following lipid peroxidation has remained elusive; (2) the lack of suitable biomarkers for preventing or prognosticating MSK diseases; (3) the inadequate exploration of ferroptosis inducers or inhibitors regarding conditions of application, initiation time point, dose, administration form, and duration; (4) the current understanding of ferroptosis in MSK diseases primarily relies on data from animal or cellular studies; and (5) crosstalk exists between key regulatory factors of ferroptosis (e.g., SLC7A11, GPx4, Nrf2) and other types of PCD (e.g., autophagy and apoptosis).

Understanding the network organization of the ferroptosis system is pivotal for comprehending the mechanisms underlying ferroptosis, rather than solely focusing on the effects of individual regulators. Investigating the ferroptotic network will not only illuminate the treatment and diagnosis of MSK diseases but also yield valuable insights into the latent mechanisms involved in their onset and progression. Hence, additional research is imperative to elucidate the underlying mechanisms of ferroptosis in MSK diseases.

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Siyang Cao: Writing – original draft, Formal analysis, Conceptualization. **Yihao Wei:** Writing – original draft, Investigation, Data curation. **Yaohang Yue:** Writing – review & editing, Software, Methodology. **Peng Liu:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Hui Zeng:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

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.

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Appendix A. Supplementary data

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