Original Article

A bibliometric analysis of the literature published on autophagy, ferroptosis, necroptosis, and pyroptosis in cardiovascular disease from 2009 to 2023

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Background: Programmed cell death (PCD) plays a pivotal role in the development and progression of cardiovascular disease (CVD), which remains the leading cause of mortality worldwide. Among the various types of PCD, autophagy, ferroptosis, necroptosis, and pyroptosis have garnered increasing attention due to their involvement in inflammation, oxidative stress, and cardiomyocyte survival. Although numerous studies have explored the underlying mechanisms of these pathways, their therapeutic potential in clinical practice remains limited. With the rapid growth of publications in this field, a comprehensive understanding of research trends and influential studies is essential to guide future investigations. This study aimed to characterize the progress and research hotspots of autophagy in CVD, ferroptosis in CVD, necroptosis in CVD, and pyroptosis in CVD through a bibliometric analysis to provide a comprehensive overview of PCD in CVD.

Methods: Publications from January 1, 2009, to December 31, 2023, were analyzed using the "bibliometrix" R package to assess research output, key contributors, and influential journals in each field.

Results: For the topic of autophagy in CVD, 6,426 articles published by 4,891 institutions from 90 countries/regions were retrieved. For the topic of necroptosis in CVD, 393 articles from 616 organizations in 53 countries/regions were retrieved. For the topic of pyroptosis in CVD, 640 publications from 754 institutions in 48 countries/regions were retrieved. Finally, for the topic of ferroptosis in CVD, 687 articles from 827 institutions in 49 countries/regions were retrieved. Key contributors included Adriana A (22 publications on necroptosis), Ge J, and Ye B (8 publications each on pyroptosis), and Ren J (lead contributor in autophagy and ferroptosis, with 120 and 10 publications, respectively). The most frequently co-cited journals were *Cell*, *Nature*, *Free Radical Biology and Medicine*, and the *Journal of Biological Chemistry*.

Conclusions: This bibliometric analysis highlights the growing interest in PCD in CVD research, with autophagy and pyroptosis being the central themes. Future studies should examine therapeutic strategies targeting ferroptosis and necroptosis to improve CVD treatment. The findings provide a roadmap for researchers to navigate emerging research hotspots and foster interdisciplinary collaboration.

Keywords: Autophagy; ferroptosis; pyroptosis; cardiovascular disease (CVD)

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Introduction

Heart disease is the predominant cause of global mortality (1). Cardiomyocytes are terminally differentiated cells which have limited capacity for differentiation (2), and there is little that can be done once cell death occurs in cardiomyocytes. Abnormal cell death of cardiomyocytes has been implicated in the majority of cardiovascular diseases (CVDs). For instance, the critical event leading to ischemic myocardial injury and heart failure involves the cardiomyocyte death.

Initially, cell death was regarded as an unregulated process. However, a recent research has revealed that cell death is regulated, involving intricate biological processes mediated by numerous molecules and pathways (3). Regulated cell death can be divided into the apoptotic and non-apoptotic types, including autophagy, necroptosis, ferroptosis, pyroptosis, and cuproptosis. Autophagy is a cellular process by which cellular components are captured by autophagosomes and then merged with the lysosome to be degraded (4). Excessive activation of autophagy leads to cell death. Necroptosis is a form of cell death regulated by receptor-interacting protein kinase 1 (RIPK1), receptor-interacting protein kinase 3 (RIPK3), and mixed-lineage kinase domain-like protein (MLKL) (5). Ferroptosis is a type of regulated cell death characterized by iron-dependent lipid peroxidation (6). Glutathione peroxidase 4 (GPX4) and the ferroptosis suppressor protein 1 (FSP1) are key enzymes that suppress ferroptosis by neutralizing lipid peroxides (7). Pyroptosis is a highly regulated cell death characterized by gasdermin D (GSDMD) or gasdermin E (GSDME)-mediated necrosis, with the inflammatory response and typical morphological changes including bubble-like formation, pore formation, and cell swelling (8,9).

The roles of autophagy, ferroptosis, necroptosis, and pyroptosis have emerged across various aspects of cardiovascular research, with each mechanism exhibiting distinct functional relevance depending on the specific disease. The role of autophagy varies significantly across different stages of disease progression and among different cell types (10). Autophagy in myocardial ischemia-reperfusion (I/R) injury acts like a double-edged sword, initially serving as a cellular quality control and survival mechanism, but eventually turning into a harmful process (11-13). Inhibition of necroptosis, ferroptosis and pyroptosis have been shown to confer significant protective effects in various CVDs, including myocardial infarction, atherosclerosis, and abdominal aortic aneurysm (14-16). Necrostatin-1, a necroptosis inhibitor, can potentially mitigate cell loss in the ischemic heart; however, further pre-clinical studies are needed before it could be approved for clinical trials (17,18). Deferiprone (Ferriprox), is a US Food and Drug Administration (FDA)-approved drug used to remove excessive iron from the body of patients with acute myocardial infarction; its mechanism involves the targeting of intramyocardial hemorrhage and suppressing cardiac hypertrophy via the reduction of ferroptosis (19,20). Inhibition of GSDMD significantly reduces cardiomyocyte pyroptosis and I/R-induced myocardial injury (21,22). The data published thus far strongly suggest that autophagy, necroptosis, pyroptosis, and ferroptosis play crucial roles in the development of CVD.

Highlight box

Key findings

- This review completed a comprehensive bibliometric analysis of the literature on programmed cell death (PCD) in cardiovascular disease (CVD) published from 2009 to 2023. The findings highlight significant research trends, influential publications, and emerging hotspots in the fields of autophagy, ferroptosis, necroptosis, and pyroptosis in CVD. The growing impact of machine learning and pharmacological interventions in understanding and targeting these cell death mechanisms emerged as a major theme.

What is known and what is new?

- Autophagy, ferroptosis, necroptosis, and pyroptosis have been implicated in various pathological processes, influencing inflammation, oxidative stress, and cardiomyocyte survival.
- This review mapped the research landscape of PCD in CVD, identifying influential studies, key contributors, and collaborative networks.

What is the implication, and what should change now?

- Greater interdisciplinary collaboration is required to develop innovative interventions that modulate PCD pathways effectively.
- Future research should focus on optimizing pharmacological strategies targeting PCD to improve cardiovascular outcomes.

Despite the growing number of studies in this field, a comprehensive and quantitative analysis of the research landscape—including trends, collaborative networks, and emerging hotspots—remains lacking. Bibliometric analysis is a powerful tool that integrates mathematics, statistics, and literature science to assess the impact and evolution of research across disciplines (23). It enables researchers to identify key trends, influential authors and publications, and forecast future directions in each field.

In this study, we conducted a comprehensive bibliometric analysis of publications related to autophagy, necroptosis, ferroptosis, and pyroptosis in CVD from January 1, 2009 to December 31, 2023. Our goal is to uncover research trends, identify leading countries/regions, institutions, authors, journals, and co-citation patterns, and to map the knowledge structure and hotspots in this field. By addressing this gap, our study provides an in-depth overview that may guide future basic and translational research in CVD. We present this article in accordance with the BIBLIO reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2025-682/rc).

Methods

Data collection

The keywords "ferroptosis and cardiovascular", "necroptosis and cardiovascular", "pyroptosis and cardiovascular", and "autophagy and cardiovascular" were each indexed in the Web of Science Core Collection (WoSCC).

On January 2024, we searched the WoSCC for literature published from 2009 to 2023 using the following search formula: "TS = (cardiovascular or heart or circulation) AND TS = (ferroptosis)", "TS = (cardiovascular or heart or circulation) AND TS = (autophagy)", "TS = (cardiovascular or heart or circulation) AND TS = (Pyroptosis)", and "TS = (cardiovascular or heart or circulation) AND TS = (Necroptosis)". In total, 687 articles related to ferroptosis in CVD, 393 articles related to necroptosis in CVD, 640 articles related to pyroptosis in CVD, and 6,426 articles related to autophagy in CVD were retrieved, and the records were exported with all references, saved as plain text files, and stored in saved recs_text format.

Only peer-reviewed journal articles were included, while grey literature such as preprints, conference abstracts, and unpublished studies were excluded. Citation analysis, co-authorship networks, and journal co-citation patterns were used to identify the influential authors, institutions, and research hotspots. Only studies published in the English language were included in the analysis. No additional contact with study authors or trial registries was required.

To ensure the accuracy and consistency of the review, the selected papers were independently assessed by Haiyan Zhou, Y.Z. and T.L. Each paper was evaluated based on predefined criteria, including relevance to the research questions, study quality, and methodological rigor. The assessment was guided by a standardized checklist to minimize bias and ensure a systematic evaluation (Figure S1).

Statistical analysis

The "bibliometrix" R package (The R Foundation for Statistical Computing, Vienna, Austria) was used to download and analyze the general information of the literature, including year of publication, country, organization, journal, and author. Subsequently, VOSviewer software version 1.6.18 (Leiden University's Centre for Science and Technology Studies, Leiden, the Netherlands) was employed to conduct bibliometric and visualization analysis. The review included co-authorship, co-occurrence, citation, bibliographic coupling, and co-citation analyses. For co-authorship analysis, the relevance of papers was determined according to the number of co-authored documents. For co-occurrence analysis, the relevance of papers was determined according to the number of documents they co-occurred in. For citation analysis, the relevance was determined according to the number of citations. For bibliographic coupling analysis, the relevance of papers was determined according to the number of shared citations of the analyzed papers. For co-citation analysis, the relevance of papers was determined by the number of times two appeared papers in the same document. Ranking was based on a counting method, and the association strength was normalized in VOSviewer software. Microsoft Office Excel 2019 (Microsoft Corp., Redmond, WA, USA) was used to analyze the number of publications per year.

Results

The annual trends of publications

The quantity of publications during a period indicates the prevailing research interests within the field. The number of publications on autophagy in CVD, ferroptosis in CVD, necroptosis in CVD, and pyroptosis in CVD increased annually overall. For autophagy, the volume of literature

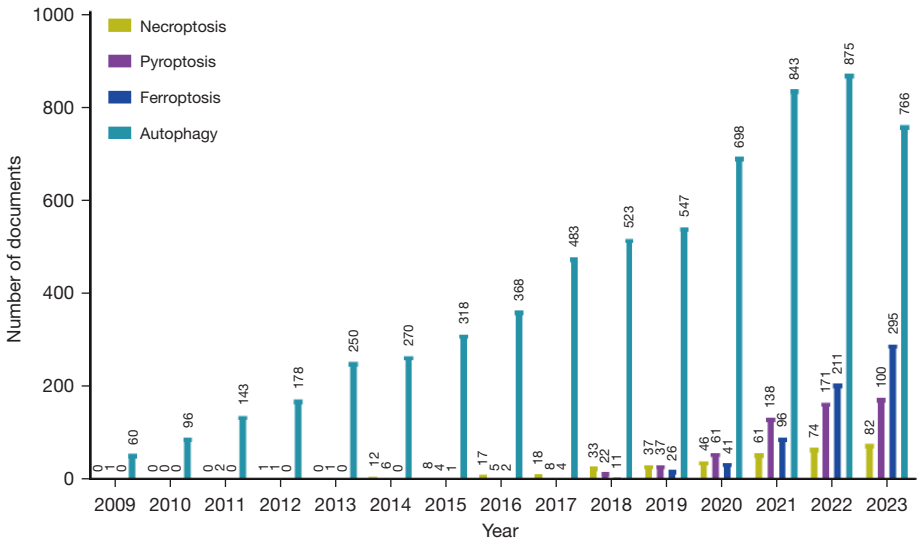

Figure 1 Number of articles published annually. Publication trend in the fields of autophagy in cardiovascular disease, ferroptosis in cardiovascular disease, necroptosis in cardiovascular disease, and pyroptosis in cardiovascular disease from 2009 to 2023.

increased steadily from 2009 to 2021 but remained stagnant from 2021 to 2023. The volume of literature on necroptosis CVD increased steadily year by year from 2013 to 2023. For ferroptosis in CVD, the volume of literature grew rapidly year to year starting in 2015. Similar to ferroptosis in CVD, the number of publications on pyroptosis in CVD increased gradually beginning in 2012 (*Figure 1*).

Distribution of countries/regions and organizations

For autophagy in CVD, 4,891 institutions from 90 different countries/regions published 6,426 articles. In the field of necroptosis CVD, 393 articles were published from 616 organizations in 53 countries/regions. For pyroptosis in CVD, 754 institutions from 48 various countries/regions contributed 640 publications. Ferroptosis in CVD, 687 articles were published from 827 institutions in 49 countries/regions. Both China and the United States ranked as top countries in the number of articles and total citations related to autophagy, necroptosis, pyroptosis, and ferroptosis in CVD. All the top 10 institutions, except for Comenius University Bratislava, University of Washington Seattle, Slovak Academy of Sciences, Chiang Mai University, Virginia Commonwealth University, and the University of Nicosia, were from China. In the fields of necroptosis in CVD, Comenius University Bratislava ranked first in the number of articles. Meanwhile, Harbin Medical University achieved the top rank in terms of the number of publications on pyroptosis in CVD factor (CVDF). Fudan University ranked the first in the number of publications in the field of autophagy in CVD. For ferroptosis in CVD, Zhejiang University contributed to the largest number of publications (*Table 1*).

Cooperation between countries/regions, as indicated by co-authorship (Figure S2), citation (Figure S3), and bibliographic coupling analyses (Figure S4), was mainly observed between China and the United States, with limited cooperation evident between other nations. The collaboration between institutions, as indicated by co-authorship (Figure S5), citation (Figure S6), and bibliographic coupling analyses (Figure S7), was more complex. Large institutions had a diversity of connections with other organizations; however, some organizations remain isolated.

Co-authorship, citation, bibliographic coupling, and co-citation analyses for authors

In the fields of necroptosis in CVD, pyroptosis in CVD, ferroptosis in CVD, and autophagy in CVD, there were 2,435, 4,125, 4,432, and 31,253 authors involved in the publications, respectively. In the field of necroptosis in CVD, Adameova A published the highest number of papers (n=22), followed by Adrian A (14) and Zhang W (12). In the field of pyroptosis in CVD, Ge J and Ye B ranked first in the number of publications, each with 8 papers published.

Table 1 The top 10 countries and organizations ranked based on the number of publications in the field of necroptosis, pyroptosis, ferroptosis, and autophagy in cardiovascular disease

Type	Rank	Country				Organization			
		Country	Avg.pub. year	Documents	Citations	Organization	Avg.pub. year	Documents	Citations
Necroptosis	1	China	2021	199	6,056	Comenius University Bratislava	2019	22	697
	2	USA	2019	96	7,041	Nantong University	2020	15	265
	3	Slovakia	2019	23	3,730	Fudan University	2021	15	330
	4	Germany	2018	25	697	Central South University	2020	12	233
	5	Canada	2020	21	742	University of Washington Seattle	2020	11	769
	6	England	2022	18	468	Slovak Academy of Sciences	2021	10	207
	7	Japan	2020	14	570	Chiang Mai University	2022	9	97
	8	India	2021	10	213	Nanchang University	2021	9	311
	9	Thailand	2022	10	229	Chinese Academy of Medical Sciences	2022	9	716
	10	Russia	2020	9	471	Capital Medical University	2022	8	83
Pyroptosis	1	China	2022	482	10,898	Harbin Medical University	2021	39	1,618
	2	USA	2019	99	8,641	Fudan University	2021	22	682
	3	England	2020	19	722	Sun Yat Sen University	2021	21	788
	4	Germany	2020	17	1,680	Nanjing Medical University	2022	20	432
	5	Italy	2022	13	466	Wenzhou Medical University	2021	18	384
	6	India	2022	11	73	Zhejiang University	2022	18	140
	7	Russia	2022	10	259	University of South China	2022	18	551
	8	Spain	2021	10	413	Chinese Academy of Medical Sciences	2021	17	331
	9	Japan	2020	10	671	Shanghai Jiao Tong University	2022	16	233
	10	Canada	2021	8	321	Wuhan university	2022	15	539
Ferroptosis	1	China	2022	522	12,886	Zhejiang University	2022	28	2,092
	2	USA	2021	99	8,550	Wuhan university	2022	26	678
	3	Japan	2021	22	1,204	Fudan University	2022	23	590
	4	Germany	2020	20	2,494	Central South University	2022	22	704
	5	Canada	2021	14	404	Nanjing Medical University	2022	21	250
	6	Italy	2022	10	516	Southern Medical University	2022	19	221
	7	Russia	2022	10	323	Shanghai Jiao Tong University	2022	18	1,373
	8	India	2022	9	259	Harbin Medical University	2022	17	177
	9	Korea	2021	9	225	Nanchang University	2022	17	182
	10	Iran	2022	9	39	Huazhong University of Science and Technology	2022	16	209
Autophagy	1	China	2020	3099	73,121	Fudan University	2019	191	5,358
	2	USA	2017	1833	97,772	Shanghai Jiao Tong University	2019	131	4,644
	3	Italy	2019	329	16,139	Air Force Military Medical University	2018	125	5,489
	4	Japan	2017	294	16,195	Shandong University	2019	121	3,232

Table 1 *(continued)*

Table 1 *(continued)*

Type	Rank	Country				Organization			
		Country	Avg.pub. year	Documents	Citations	Organization	Avg.pub. year	Documents	Citations
	5	Germany	2017	276	14,707	Capital Medical University	2019	118	2,980
	6	England	2018	214	15,389	University of Wyoming	2014	103	5,240
	7	Canada	2017	203	10,465	Nanjing Medical University	2019	103	2,353
	8	France	2019	164	8,901	Zhejiang University	2021	101	3,251
	9	India	2020	145	5,231	Wuhan university	2020	100	2,135
	10	Spain	2019	145	3,729	Huazhong University of Science and Technology	2020	95	2,149

Avg.pub.year, average publication year.

In the field of autophagy in CVD and ferroptosis in CVD, Ren J ranked first with 120 papers published and 10 papers published, respectively (*Table 2*, Figures S8,S9, *Figure 2*). Co-cited authors are authors who are cited in the same paper, forming a co-citation relationship.

In the fields of necroptosis in CVD, pyroptosis in CVD, ferroptosis in CVD, and autophagy in CVD, there were 16,024, 24,681, 26,648, and 138,237 co-cited authors involved in the publication of literature, respectively (*Table 2*, *Figure 3*). In the field of necroptosis in CVD, Degterev A was the most cited author (157 times), followed by Linkermann A (138 times) and Zhang T (134 times). In the field of pyroptosis in CVD, Shi JJ ranked first with 273 citations, followed by Zhang Y (179 times) and Toldo S (175 times). In the field of ferroptosis in CVD, Dixon SJ had the most citations (542 times), followed by Fang XX (438 times) and Yang WS (420 times). Mizushima N was cited 1,579 times and was ranked first in the field of autophagy in CVD, followed by Levine B (1,052 times) and Klionsky DJ (905 times).

Citation, bibliographic, and co-citation analyses for journals

In the field of necroptosis in CVD, 220 journals published 393 articles. In the field of pyroptosis in CVD, 290 journals published 640 articles. In the field of ferroptosis in CVD, 297 journals published 687 papers. In the field of autophagy in CVD, 1,245 journals published 6,426 papers. *The International Journal of Molecular Sciences* published 13 papers, placing it first place in the field of necroptosis in CVD, followed by *Frontiers in Cardiovascular Medicine* (12 articles) and *Frontiers in Pharmacology* (10 articles). In the field of pyroptosis in CVD, 24 papers were published in *Frontiers in Cardiovascular Medicine* which had the highest number of articles, followed by *Oxidative Medicine and Cellular Longevity* (17 articles) and *Cell Death & Disease* (16 articles). In the field of ferroptosis in CVD, *Frontiers in Cardiovascular Medicine* had the highest number of publications (29 articles), followed by *Frontiers in Pharmacology* (23 articles) and *Free Radical Biology and Medicine* (19 articles). In the field of autophagy in CVD, the *International Journal of Molecular Sciences* had 136 papers, placing it first, followed by *Circulation* (134 articles) and the *Journal of Molecular and Cellular Cardiology* (128 articles). In the field of necroptosis in CVD, ferroptosis in CVD, and autophagy in CVD, *Circulation* (Q1) had the highest impact factor (IF; 39.918). In the field of pyroptosis in CVD, *Cell Death & Disease* (Q2) had the highest IF (12.100) (*Table 3* and *Figure 4*, Figure S10).

Journal co-citation analysis is a valuable tool for examining which journals are frequently cited together. The results of our co-citation analysis indicated that in the field of necroptosis in CVD, *Cell* and *Nature* were the two most cited journals. In the field of pyroptosis in CVD, *Nature* and *Circulation* were two most cited journals (over 1,000 citations). In the field of ferroptosis in CVD, *Free Radical Biology and Medicine* and *Nature* were two most cited journals (over 1,000 citations). In the field of autophagy in CVD, *the Journal of Biological Chemistry* and *Circulation Research* were the two most cited journals (over 1,000 citations) (*Table 3*, *Figure 5*).

Citations and co-citations

In the field of necroptosis in CVD, the article "CaMKII is

Table 2 The top 10 co-cited authors in the field of necroptosis, pyroptosis, ferroptosis, and autophagy in cardiovascular disease

Type	Rank	The top 10 authors				The top 10 Co-cited author	
		Author	Avg.pub.year	Documents	Citations	Co-cited author	Citations
Necroptosis	1	Adameova, Adriana	2019	22	625	Degterev, A	157
	2	Szobi, Adrian	2017	14	287	Linkermann, A	138
	3	Zhang, Wei	2021	12	106	Zhang, T	134
	4	Chattipakorn, Nipon	2021	9	97	Galluzzi, L	128
	5	Chattipakorn, Siriporn C	2021	9	97	He, SD	99
	6	Maneechote, Chayodom	2022	8	65	Newton, K	94
	7	Zhang, Jingjing	2018	7	7	Zhou, H	89
	8	Qian, Jianan	2022	7	7	Cho, Y	81
	9	Arunsak, Busarin	2023	7	44	Luedde, M	81
	10	Horvath, Csaba	2022	7	64	Sun, LM	80
Pyroptosis	1	Ge, Junbo	2021	8	239	Shi, JJ	273
	2	Ye, Bozhi	2022	8	211	Zhang, Y	179
	3	Dai, Shanshan	2022	7	210	Toldo, S	175
	4	Mishra, Paras K.	2019	7	225	Kayagaki, N	135
	5	Wang, Hong	2021	7	403	Liu, X	123
	6	Yang, Wei	2021	7	149	Lamkanfi, M	118
	7	Zhang, Jing	2022	7	165	Wang, Y	116
	8	Huang, Weijian	2022	6	144	Liu, Y	107
	9	Abbate, Antonio	2021	6	944	Zeng, ZL	107
	10	Jiang, Xiaohua	2020	6	402	Li, X	101
Ferroptosis	1	Ren, Jun	2022	10	204	Dixon, SJ	542
	2	Matsui, Takashi	2020	9	463	Fang, XX	438
	3	Li, Wei	2022	9	239	Yang, WS	420
	4	Chattipakorn, Nipon	2022	9	88	Stockwell, BR	288
	5	Higa, Jason K.	2019	8	443	Gao, MH	281
	6	Min, Junxia	2022	7	1,908	Doll, S	250
	7	Wang, Fudi	2022	7	1,908	Angeli, JPF	210
	8	Peng, Jun	2022	7	356	Chen, X	202
	9	Liu, Ying	2023	7	155	Wang, Y	152
	10	Chattipakorn, Nipon	2022	7	81	Li, N	146
Autophagy	1	Ren, Jun	2016	120	5,368	Mizushima, N	1,579
	2	Sadoshima, Junichi	2018	106	7,364	Levine, B	1,052
	3	Zhang, Yingmei	2017	57	3,027	Klionsky, DJ	905
	4	Gottlieb, Roberta A.	2014	53	3,511	Sciarretta, S	877

Table 2 *(continued)*

Table 2 *(continued)*

Type	Rank	The top 10 authors				The top 10 Co-cited author	
		Author	Avg.pub.year	Documents	Citations	Co-cited author	Citations
	5	Hill, Joseph A.	2013	48	3,832	Matsui, Y	775
	6	Gustafsson, Asa B.	2014	46	3,777	Nakai, A	685
	7	Sciarretta, Sebastiano	2015	40	3,874	Wang, Y	680
	8	Zhai, Peiyong	2015	39	3,295	Zhang, Y	637
	9	Kroemer, Guido	2019	38	2,577	Kim, J	607
	10	Lavandero, Sergio	2016	35	2,190	Chen, Y	527

Avg.pub.year, average publication year.

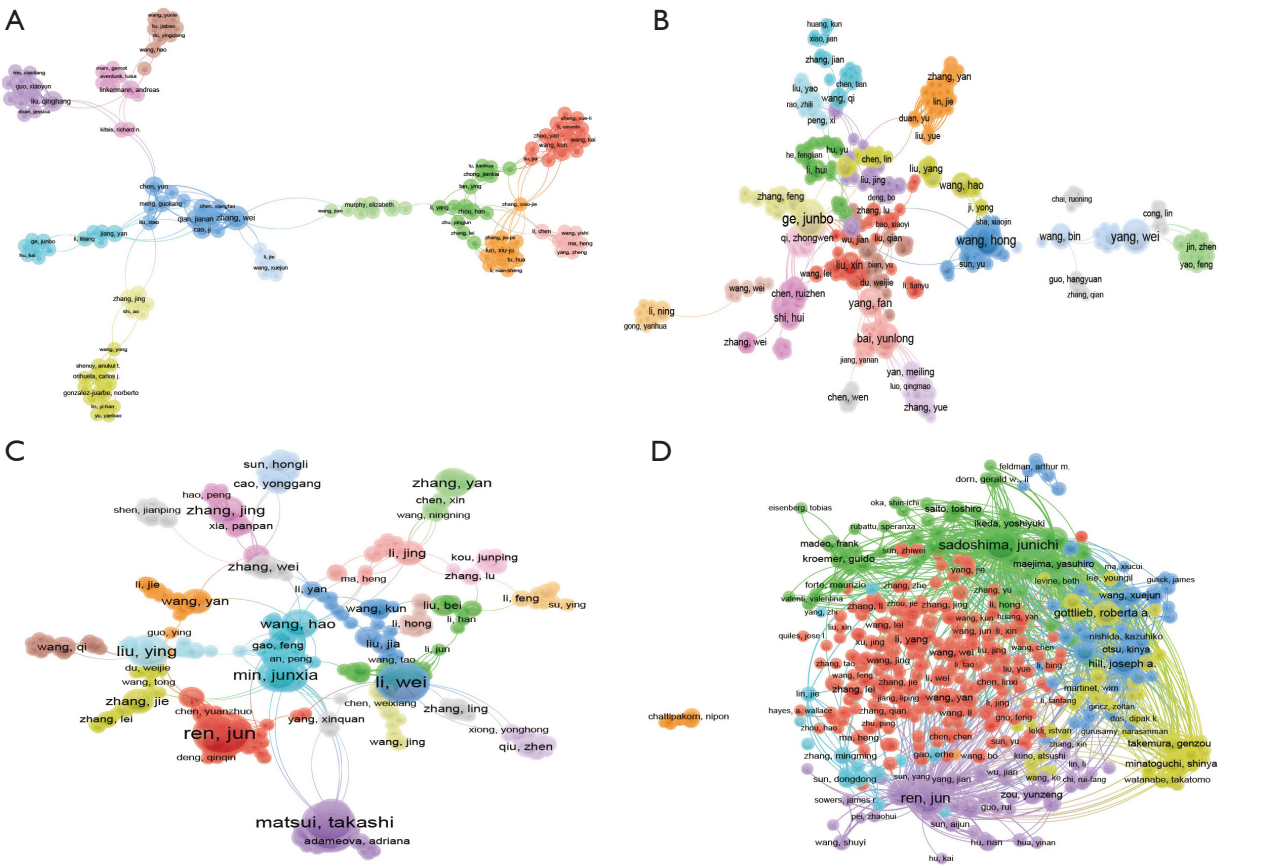

Figure 2 VOSviewer visualization map of the bibliographic coupling analysis for authors. (A) Necroptosis in cardiovascular disease. (B) Pyroptosis in cardiovascular disease. (C) Ferroptosis in cardiovascular disease. (D) Autophagy in cardiovascular disease.

a RIP3 substrate mediating ischemia- and oxidative stress-induced myocardial necroptosis" was the most cited paper (514 citations) (24). For pyroptosis in CVD, the article "Pyroptosis: host cell death and inflammation" was the most cited paper (2,105 citations) (25). In the field of ferroptosis in CVD, the article "Ferroptosis as a target for protection against cardiomyopathy" published in *Cell Death and Differentiation* was cited 1,959 times (26), placing it first in

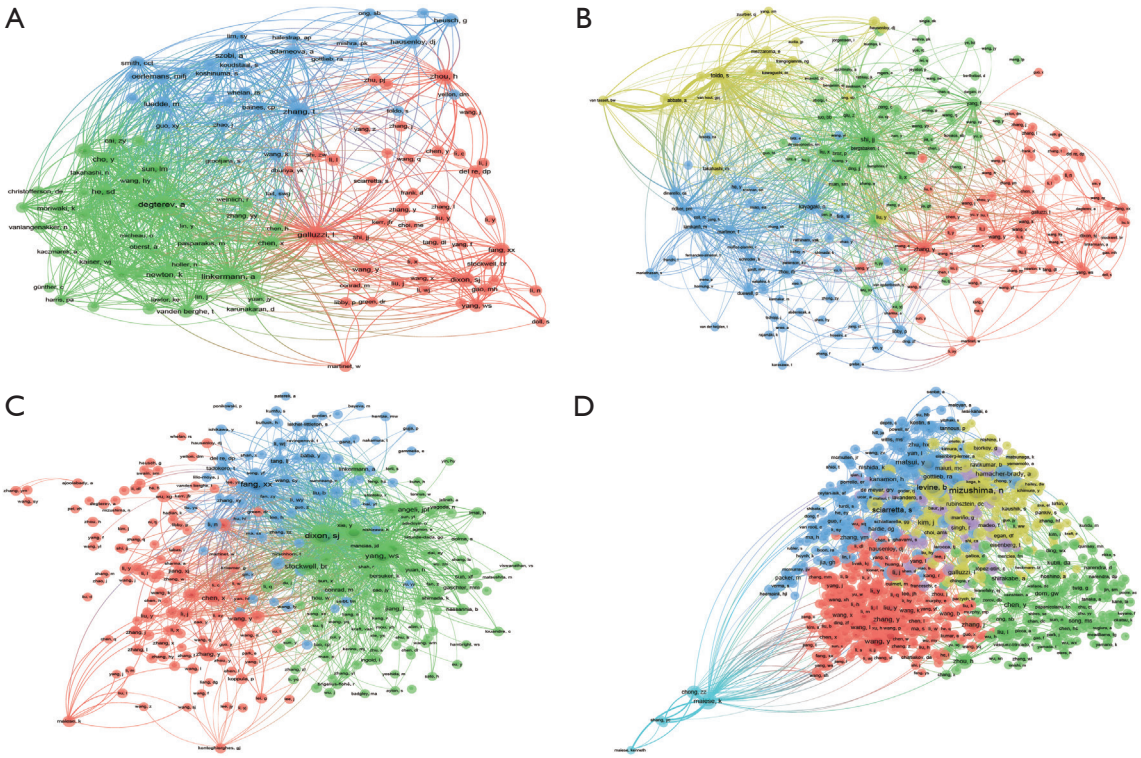

Figure 3 VOSviewer visualization map of the co-citation analysis for authors. (A) Necroptosis in cardiovascular disease. (B) Pyroptosis in cardiovascular disease. (C) Ferroptosis in cardiovascular disease. (D) Autophagy in cardiovascular disease.

the field. The most cited publication in autophagy in CVD was the article "Cardioprotection and lifespan extension by the natural polyamine spermidine" published in *Nature Medicine* (27) (*Table 4*, *Figures 6*,7).

Table 5 and *Figure 8* list the top 10 references with the most co-citations in the field of necroptosis in CVD, pyroptosis in CVD, ferroptosis in CVD, and autophagy in CVD. As shown in *Table 5*, the paper with most co-citations in the field of necroptosis in CVD was by Zhang *et al.* who identified CaMKII as a novel substrate of RIP3, outlining a RIP3-CaMKII-mPTP pathway involved in myocardial necroptosis (24). The article with the most co-citations in the field of pyroptosis in CVD found that GSDMD plays a critical role in caspase-11 and caspase-1-mediated pyroptosis in mouse bone marrow macrophages. In the field of ferroptosis in CVD, the article with the most co-citations was by Dixon *et al.* (73), who identified ferrostatin-1 as a strong inhibitor of ferroptosis in cancer cells and of glutamate-induced cell death in organotypic rat brain slices, indicating potential similarities between these two processes. In the field of autophagy in CVD, the article with the most co-citations was Nakai *et al.* (78) who found that autophagy in the heart under normal conditions acts as a homeostatic mechanism to maintain the size of cardiomyocytes and overall cardiac structure and function; additionally, they found that increased autophagy in failing hearts serves as an adaptive response to protect cells from the stress caused by hemodynamic changes.

Table S1 and Figure S11 list the top 10 keywords most common keywords for the field of necroptosis in CVD, pyroptosis in CVD, ferroptosis in CVD, and autophagy in CVD. In the field of necroptosis in CVD, the top 10 keywords were "necroptosis", "apoptosis", "cell-death", "oxidative stress", "necrosis", "inflammation", "autophagy", "heart", "activation", and "programmed necrosis". In the field of pyroptosis CVD, "pyroptosis", "nlrp3 inflammasome", "activation", "apoptosis", "oxidative stress", "inflammation", "cell-death", "atherosclerosis", "mechanisms", and "autophagy" were the top 10 keywords. For ferroptosis in CVD, "ferroptosis", "oxidative stress", "cell death", "iron", "apoptosis", "mechanisms", "lipid peroxidation", "heart", "metabolism", and "autophagy" were the top 10 keywords. Finally, in the field of autophagy in CVD, "autophagy", "apoptosis", "oxidative stress",

Table 3 The top 10 co-cited journals in the field of necroptosis, pyroptosis, ferroptosis, and autophagy in cardiovascular disease

Type	Rank	The top 10 journal					The top 10 co-cited journal			
		Journal	Documents	Citation	IF [2023]	JCR	Co-cited journal	Citation	IF [2023]	JCR
Necroptosis	1	*International Journal of Molecular Sciences*	13	165	6.208	Q2	*Cell*	858	64.500	Q1
	2	*Frontiers in Cardiovascular Medicine*	12	164	3.600	Q2	*Nature*	762	63.580	Q1
	3	*Frontiers in Pharmacology*	10	277	4.225	Q1	*Cell Death & Difference*	708	12.067	Q2
	4	*Oxidative Medicine and Cellular Longevity*	8	92	7.310	Q2	*Proceedings of the National Academy of Sciences of the United States of America*	689	12.779	Q1
	5	*Journal of Cellular and Molecular Medicine*	7	189	4.302	Q2	*Circulation*	664	39.918	Q1
	6	*Journal of Molecular and Cellular Cardiology*	7	258	5.700	Q2	*Circulation Research*	632	20.100	Q1
	7	*Biomedicine & Pharmacotherapy*	6	62	7.419	Q1	*Journal of Biological Chemistry*	605	5.486	Q2
	8	*Circulation*	6	174	39.918	Q1	*Cell Death & Disease*	510	9.685	Q2
	9	*International Journal of Molecular Medicine*	6	116	3.098	Q3	*Cardiovascular Research*	407	13.081	Q1
	10	*Molecular and Cellular Biochemistry*	6	111	3.842	Q4	*Journal of Molecular And Cellular Cardiology*	403	5.763	Q2
Pyroptosis	1	*Frontiers in Cardiovascular Medicine*	24	197	3.600	Q2	*Nature*	1,524	63.580	Q1
	2	*Oxidative Medicine and Cellular Longevity*	17	376	7.310	Q2	*Circulation*	1,004	39.918	Q1
	3	*Cell Death & Disease*	16	1,295	12.100	Q2	*Circulation Research*	935	20.100	Q1
	4	*Frontiers In Pharmacology*	16	313	5.988	Q2	*Proceedings of the National Academy of Sciences of The United States of America*	824	12.779	Q1
	5	*Biomedicine & Pharmacotherapy*	15	176	7.419	Q1	*Cell*	803	64.500	Q1
	6	*Frontiers in Cell and Developmental Biology*	15	267	6.081	Q1	*Cell Death & Disease*	744	9.685	Q2
	7	*International Journal of Molecular Sciences*	15	141	6.208	Q1	*Journal of Biological Chemistry*	721	5.486	Q2
	8	*Frontiers in Immunology*	14	713	7.561	Q1	*PLoS One*	628	3.752	Q2
	9	*International Immunopharmacology*	14	227	5.714	Q2	*Biochemical and Biophysical Research Communications*	543	3.322	Q3
	10	*Biochemical and Biophysical Research Communications*	11	231	3.300	Q3	*Oxidative Medicine and Cellular Longevity*	530	7.310	Q2

Table 3 *(continued)*

Table 3 *(continued)*

Type	Rank	The top 10 journal					The top 10 co-cited journal			
		Journal	Documents	Citation	IF [2023]	JCR	Co-cited journal	Citation	IF [2023]	JCR
Ferroptosis	1	*Frontiers in Cardiovascular Medicine*	29	300	3.600	Q2	*Cell*	1,480	64.500	Q1
	2	*Frontiers in Pharmacology*	23	479	5.988	Q2	*Free Radical Biology and Medicine*	1,306	8.101	Q2
	3	*Free Radical Biology and Medicine*	19	512	8.101	Q2	*Nature*	1,223	63.580	Q1
	4	*Biomedicine & Pharmacotherapy*	17	233	7.419	Q2	*Proceedings of the National Academy of Sciences of The United States of America*	1,127	12.779	Q1
	5	*Oxidative Medicine and Cellular Longevity*	17	351	7.310	Q2	*Journal of Biological Chemistry*	882	5.486	Q1
	6	*Frontiers in Cell and Developmental Biology*	16	341	5.500	Q3	*Cell Death & Disease*	855	9.685	Q2
	7	*International Journal of Molecular Sciences*	14	319	6.208	Q1	*Circulation*	842	39.918	Q1
	8	*Cells*	11	138	7.666	Q2	*Circulation Research*	835	20.100	Q1
	9	*Life Sciences*	9	556	6.780	Q2	*Biochemical and Biophysical Research Communications*	820	3.322	Q3
	10	*Antioxidants*	8	243	7.675	Q2	*Cell Death & Difference*	782	12.067	Q2
Autophagy	1	*International Journal of Molecular Sciences*	136	2,564	6.208	Q1	*Journal of Biological Chemistry*	12,012	5.486	Q2
	2	*Circulation*	134	3,995	39.918	Q1	*Circulation Research*	11,966	20.100	Q1
	3	*Journal of Molecular and Cellular Cardiology*	128	6,347	5.763	Q2	*Autophagy*	10,239	13.300	Q1
	4	*Frontiers in Pharmacology*	117	1,878	5.988	Q2	*Circulation*	9,868	39.918	Q1
	5	*Circulation Research*	114	12,149	20.100	Q1	*Nature*	8,510	63.580	Q1
	6	*PLoS One*	109	4,270	3.752	Q2	*Proceedings of the National Academy of Sciences of the United States of America*	8,026	12.779	Q1
	7	*Autophagy*	106	6,503	13.300	Q1	*Cell*	7,224	11.091	Q1
	8	*Oxidative Medicine and Cellular Longevity*	95	3,609	7.310	Q2	*PLoS One*	7,056	3.752	Q2
	9	*Frontiers in Cardiovascular Medicine*	94	987	3.600	Q2	*Journal of Molecular and Cellular Cardiology*	5,693	5.763	Q2
	10	*Biochemical and Biophysical Research Communications*	81	2,142	3.300	Q3	*Journal of Clinical Investigation*	5,624	19.456	Q1

IF, impact factor; JCR, Journal Citation Reports.

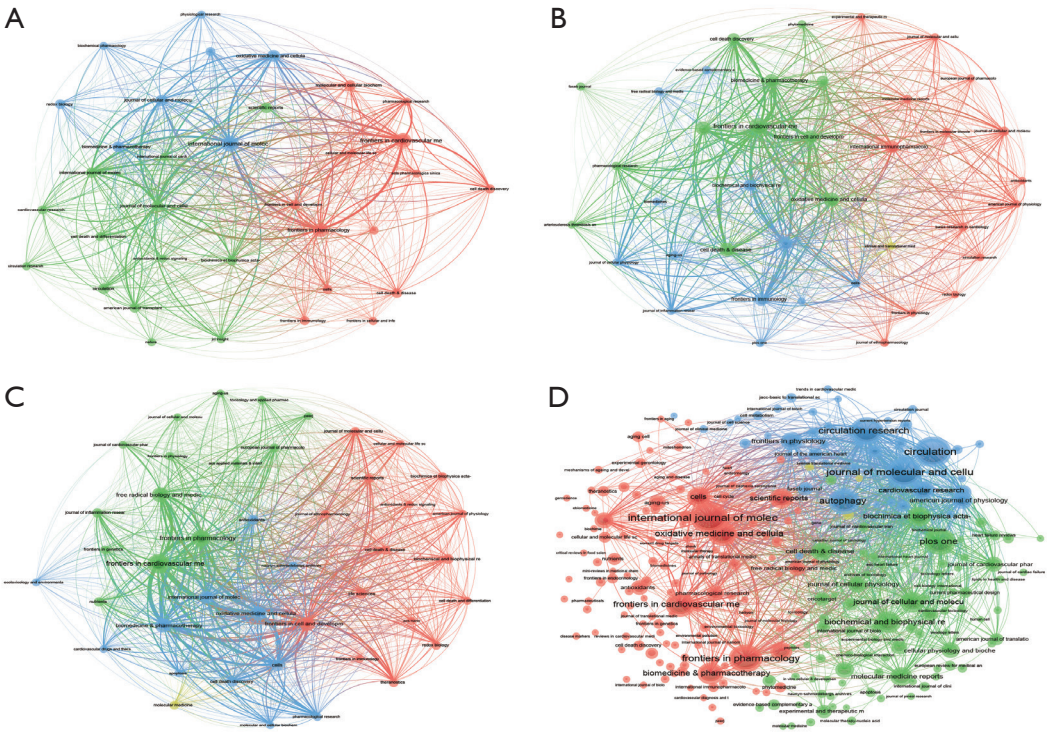

Figure 4 VOSviewer visualization map of the bibliographic coupling analysis for journals. (A) Necroptosis in cardiovascular disease. (B) Pyroptosis in cardiovascular disease. (C) Ferroptosis in cardiovascular disease. (D) Autophagy in cardiovascular disease.

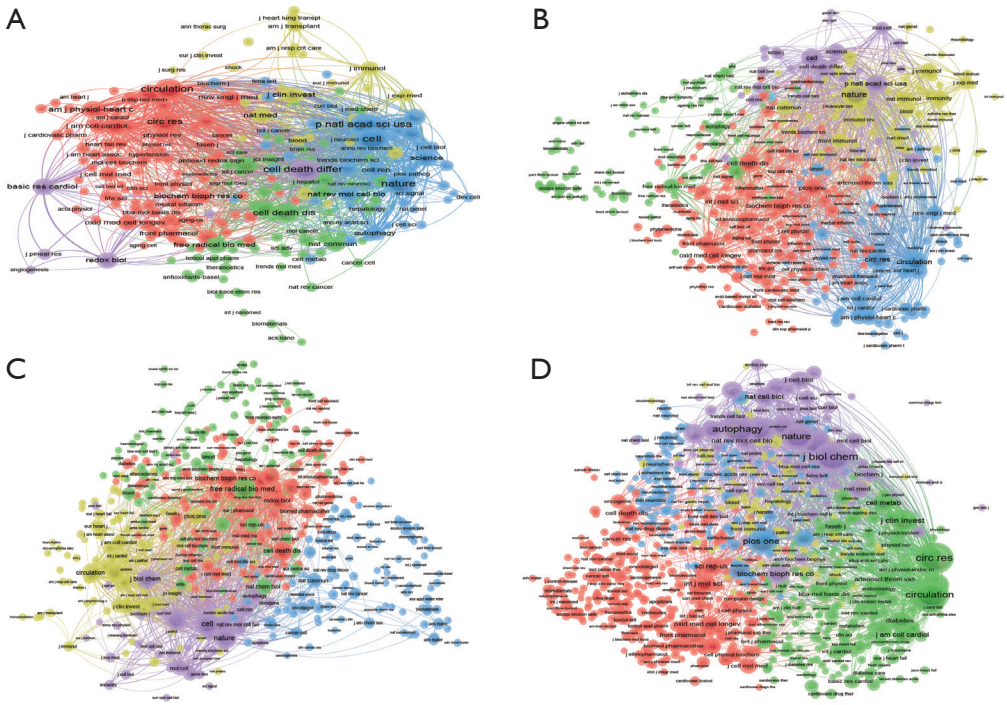

Figure 5 VOSviewer visualization map of the co-citation analysis for journals. (A) Necroptosis in cardiovascular disease. (B) Pyroptosis in cardiovascular disease. (C) Ferroptosis in cardiovascular disease. (D) Autophagy in cardiovascular disease.

Table 4 The top 10 articles in the field of necroptosis, pyroptosis, ferroptosis, and autophagy in cardiovascular disease

Type	Rank	Literature	Title	DOI	Source	IF/JCR	Citations
Necroptosis	1	Zhang T [2016]	CaMKII is a RIP3 substrate mediating ischemia- and oxidative stress-induced myocardial necroptosis (24)	10.1038/nm.4017	*Nature Medicine*	82.9/Q1	514
	2	Del Re DP [2019]	Fundamental Mechanisms of Regulated Cell Death and Implications for Heart Disease (28)	10.1152/physrev.00022.2018	*Physiological Reviews*	29.9/Q1	471
	3	Zhu P [2018]	Ripk3 promotes ER stress-induced necroptosis in cardiac IR injury: A mechanism involving calcium overload/XO/ROS/mPTP pathway (29)	10.1016/j.redox.2018.02.019	*Redox Biology*	11.4/Q1	283
	4	Luedde M [2014]	RIP3, a kinase promoting necroptotic cell death, mediates adverse remodelling after myocardial infarction (30)	10.1093/cvr/cvu146	*Cardiovascular Research*	7.0/Q1	228
	5	Qin D [2016]	MicroRNA-223-5p and -3p Cooperatively Suppress Necroptosis in Ischemic/Reperfused Hearts (31)	10.1074/jbc.M116.732735	*Journal of Biological Chemistry*	4.0/Q2	105
	6	Koshinuma S [2014]	Combination of necroptosis and apoptosis inhibition enhances cardioprotection against myocardial ischemia-reperfusion injury (32)	10.1007/s00540-013-1716-3	*Journal of Anesthesia*	2.8/Q2	96
	7	Zhe-Wei S [2018]	The Role of Necroptosis in Cardiovascular Disease (33)	10.3389/fphar.2018.00721	*Frontiers in Pharmacology*	4.4/Q1	82
	8	Guo X [2017]	Cardioprotective Role of Tumor Necrosis Factor Receptor-Associated Factor 2 by Suppressing Apoptosis and Necroptosis (34)	10.1161/CIRCULATIONAHA.116.026240	*Circulation*	35.5/Q1	66
	9	Adameova A [2016]	Necroptotic cell death in failing heart: relevance and proposed mechanisms (22)	10.1007/s10741-016-9537-8	*Heart Failure Reviews*	4.5/Q1	64
	10	Szobi A [2017]	Analysis of necroptotic proteins in failing human hearts (35)	10.1186/s12967-017-1189-5	*Journal of Translational Medicine*	6.1/Q1	55
Pyroptosis	1	Bergsbaken T [2009]	Pyroptosis: host cell death and inflammation (25)	10.1038/nrmicro2070	*Nature Reviews Microbiology*	69.2/Q1	2,105
	2	Del Re DP [2019]	Fundamental Mechanisms of Regulated Cell Death and Implications for Heart Disease (28)	10.1152/physrev.00022.2018	*Physiological Reviews*	33.6/Q1	471
	3	Mezzaroma E [2011]	The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse (36)	10.1073/pnas.1108586108	*Proceedings of the National Academy of Sciences of the United States of America*	11.2/Q1	458
	4	Wu X [2018]	Nicotine promotes atherosclerosis via ROS-NLRP3-mediated endothelial cell pyroptosis (37)	10.1038/s41419-017-0257-3	*Cell Death & Disease*	9.0/Q1	343
	5	Zhaolin Z [2019]	Role of pyroptosis in cardiovascular disease (16)	10.1111/cpr.12563	*Cell Proliferation*	8.5/Q1	241
	6	Toldo S [2018]	Inflammasome, pyroptosis, and cytokines in myocardial ischemia-reperfusion injury (38)	10.1152/ajpheart.00158.2018	*American Journal of Physiology-Heart and Circulatory Physiology*	4.1/Q1	221
	7	Li X [2014]	MicroRNA-30d regulates cardiomyocyte pyroptosis by directly targeting foxo3a in diabetic cardiomyopathy (39)	10.1038/cddis.2014.430	*Cell Death & Disease*	9.0/Q1	220
	8	Zeng C [2019]	Role of Pyroptosis in Cardiovascular Diseases and its Therapeutic Implications (40)	10.7150/ijbs.33568	*International Journal of Biological Sciences*	8.2/Q1	167

Table 4 *(continued)*

Table 4 *(continued)*

Type	Rank	Literature	Title	DOI	Source	IF/JCR	Citations
	9	Jia C [2019]	Role of pyroptosis in cardiovascular diseases (41)	10.1016/j.intimp.2018.12.028	*International Immunopharmacology*	4.8/Q1	148
	10	Shi H [2021]	GSDMD-Mediated Cardiomyocyte Pyroptosis Promotes Myocardial I/R Injury (21)	10.1161/CIRCRESAHA.120.318629	*Circulation Research*	20.1/Q1	118
Ferroptosis	1	Xie Y [2016]	Ferroptosis: process and function (42)	10.1038/cdd.2015.158	*Cell Death and Differentiation*	12.4/Q1	1,959
	2	Gao M [2015]	Glutaminolysis and Transferrin Regulate Ferroptosis (43)	10.1016/j.molcel.2015.06.011	*Molecules and Cells*	4.3/Q3	1,111
	3	Fang X [2019]	Ferroptosis as a target for protection against cardiomyopathy (26)	10.1073/pnas.1821022116	*Proceedings of the National Academy of Sciences of the United States of America*	11.2/Q1	1,019
	4	Dodson M [2019]	NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis (44)	10.1016/j.redox.2019.101107	*Redox Biology*	11.4/Q1	795
	5	Del Re DP [2019]	Fundamental Mechanisms of Regulated Cell Death and Implications for Heart Disease (28)	10.1152/physrev.00022.2018	*Physiological Reviews*	33.6/Q1	471
	6	Fang X [2020]	Loss of Cardiac Ferritin H Facilitates Cardiomyopathy via Slc7a11-Mediated Ferroptosis (45)	10.1161/CIRCRESAHA.120.316509	*Circulation Research*	20.1/Q1	329
	7	Li W [2019]	Ferroptotic cell death and TLR4/Trif signaling initiate neutrophil recruitment after heart transplantation (46)	10.1172/JCI126428	*Journal of Clinical Investigation*	15.9/Q1	263
	8	Baba Y [2018]	Protective effects of the mechanistic target of rapamycin against excess iron and ferroptosis in cardiomyocytes (2)	10.1152/ajpheart.00452.2017	*American Journal of Physiology-Heart and Circulatory Physiology*	4.1/Q1	216
	9	Park TJ [2019]	Quantitative proteomic analyses reveal that GPX4 downregulation during myocardial infarction contributes to ferroptosis in cardiomyocytes (47)	10.1038/s41419-019-2061-8	*Cell Death & Disease*	9.0/Q1	177
	10	Liu B [2018]	Puerarin protects against heart failure induced by pressure overload through mitigation of ferroptosis (48)	10.1016/j.bbrc.2018.02.061	*Biochemical and Biophysical Research Communications*	2.5/Q3	138
Autophagy	1	Eisenberg T [2016]	Cardioprotection and lifespan extension by the natural polyamine spermidine (27)	10.1038/nm.4222	*Nature Medicine*	82.9/Q1	681
	2	Bravo-San Pedro JM [2017]	Autophagy and Mitophagy in Cardiovascular Disease (49)	10.1161/CIRCRESAHA.117.311082	*Circulation Research*	20.1/Q1	479
	3	Ikeda Y [2015]	Endogenous Drp1 mediates mitochondrial autophagy and protects the heart against energy stress (50)	10.1161/CIRCRESAHA.116.303356	*Circulation Research*	20.1/Q1	411
	4	Xie Z [2011]	Improvement of cardiac functions by chronic metformin treatment is associated with enhanced cardiac autophagy in diabetic OVE26 mice (51)	10.2337/db10-0351	*Diabetes*	6.2/Q1	401
	5	Ma X [2012]	Impaired autophagosome clearance contributes to cardiomyocyte death in ischemia/reperfusion injury (52)	10.1161/CIRCULATIONAHA.111.041814	*Circulation*	35.5/Q1	379

Table 4 *(continued)*

Table 4 *(continued)*

Type	Rank	Literature	Title	DOI	Source	IF/JCR	Citations
	6	Kubli DA [2013]	Parkin protein deficiency exacerbates cardiac injury and reduces survival following myocardial infarction (53)	10.1074/jbc.M112.411363	*Journal of Biological Chemistry*	4.0/Q2	352
	7	Taneike M [2010]	Inhibition of autophagy in the heart induces age-related cardiomyopathy (54)	10.4161/auto.6.5.11947	*Autophagy*	14.6/Q1	337
	8	Sciarretta S [2018]	The Role of Autophagy in the Heart (55)	10.1146/annurev-physiol-021317-121427	*Annual Review of Physiology*	15.7/Q1	317
	9	Nishida K [2009]	The role of autophagy in the heart (56)	10.1038/cdd.2008.163	*Cell Death and Differentiation*	12.4/Q1	316
	10	Gustafsson AB [2009]	Autophagy in ischemic heart disease (57)	10.1161/CIRCRESAHA.108.187427	*Circulation Research*	20.1/Q1	314

IF, impact factor; JCR, Journal Citation Reports.

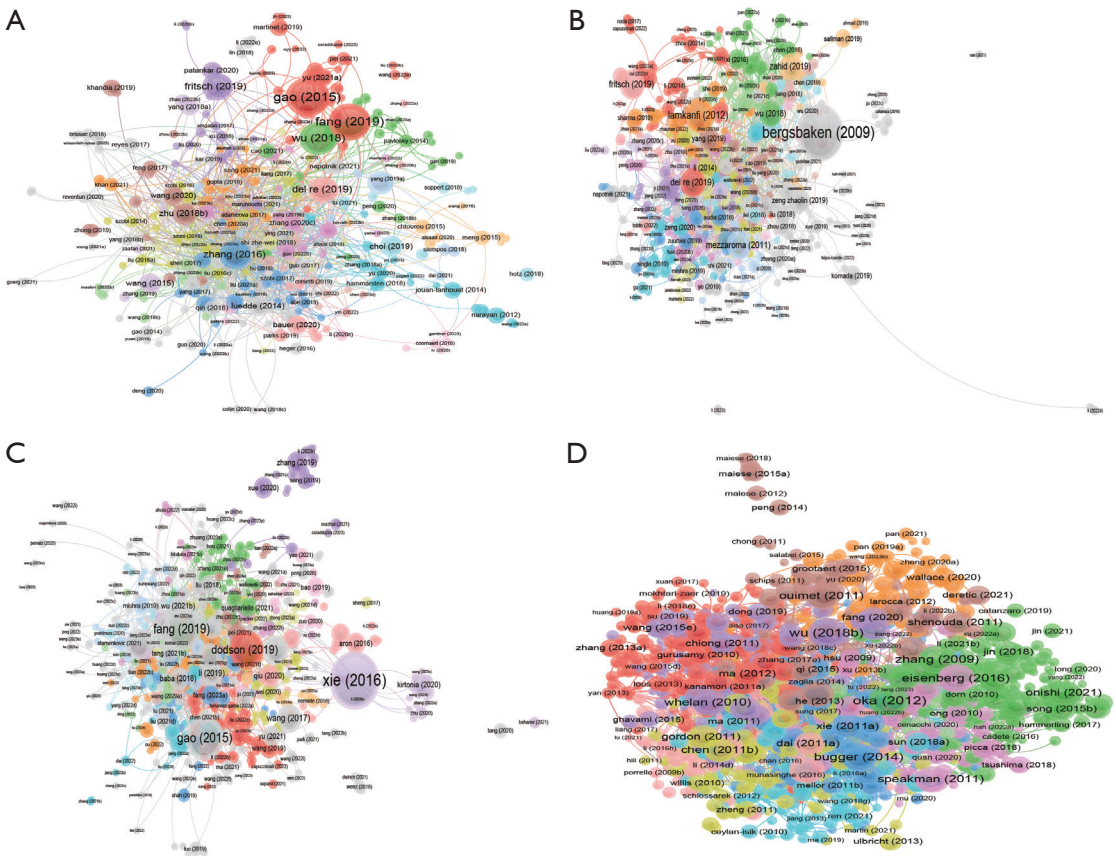

Figure 6 VOSviewer visualization map of the directly cited articles. (A) Necroptosis in cardiovascular disease. (B) Pyroptosis in cardiovascular disease. (C) Ferroptosis in cardiovascular disease. (D) Autophagy in cardiovascular disease.

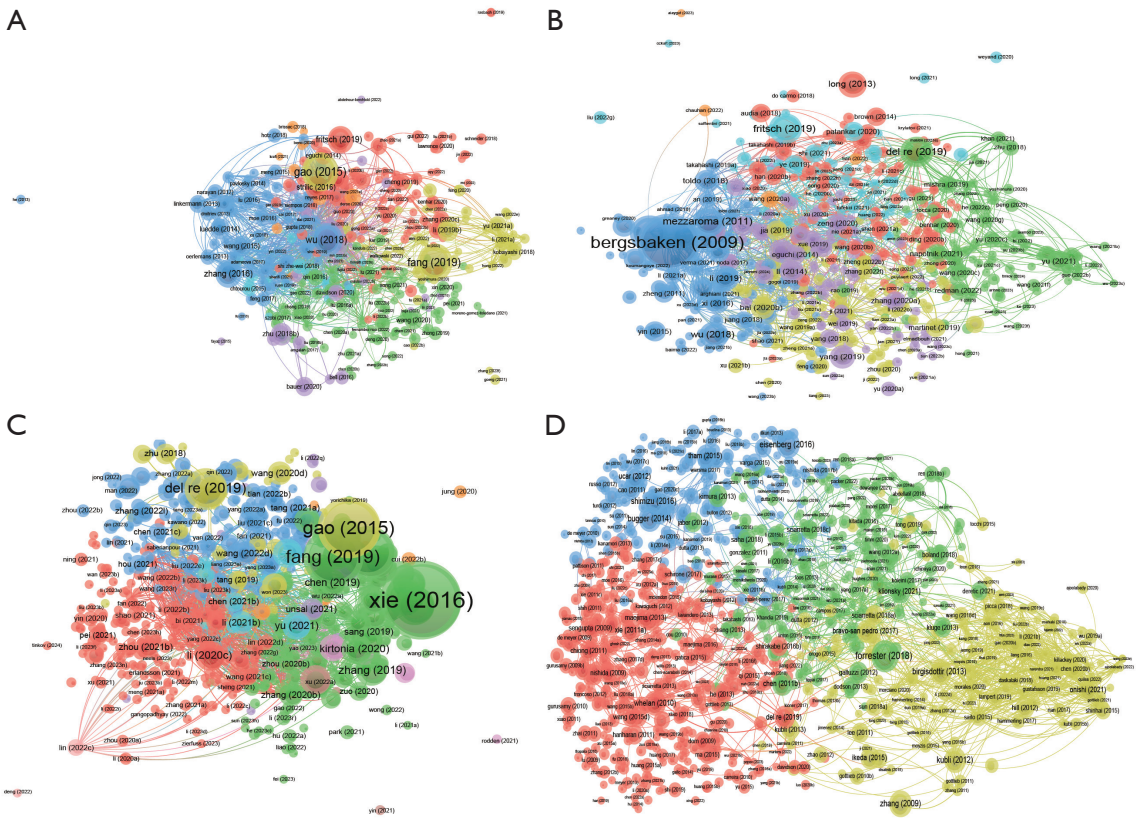

Figure 7 VOSviewer visualization map of the bibliographic coupling analysis for articles. (A) Necroptosis in cardiovascular disease. (B) Pyroptosis in cardiovascular disease. (C) Ferroptosis in cardiovascular disease. (D) Autophagy in cardiovascular disease.

"heart", "activation", "expression", "heart failure", "inflammation", "mechanisms", and "cell death" were in the top 10 keywords.

Discussion

In our study, a total of 8,146 publications were obtained from the WoSCC. Our results indicated that the number of publications on necroptosis, pyroptosis, ferroptosis, and autophagy in CVD increased annually from 2009 to 2023, especially after 2017. In the field of necroptosis in CVD, the number of publications steadily increased by approximately 10% from 2017 to 2023. Similarly, pyroptosis in CVD experienced rapid growth in publications from 2019 to 2021. In 2021, Shi *et al.* proposed that the N-terminal of GSDMD is essential for pyroptosis in cardiomyocytes and that the inhibition of GSDMD can attenuate myocardial ischemia-reperfusion injury (MIRI)-induced pyroptosis; this finding, initiated a growth in research related to pyroptosis in CVD (21,87). For ferroptosis in CVD, the number of articles increased annually by 50% between 2017 and 2023. In 2012, ferroptosis, a type of iron-dependent non-apoptotic cell death was discovered in HT-1080 and Calu-1 cells by Dixon *et al.* (73). In 2019, Fang *et al.*'s group reported that ferroptosis mediates both chemotherapy and MIRI-induced cardiomyopathy. They have further reported that heme oxygenase 1 breaks down heme and releases free iron, which subsequently causes the production of oxidized lipids in the mitochondrial membrane; moreover, iron chelation therapy can alleviate ferroptosis in cardiomyocytes (26). This article pushed the research on ferroptosis in cardiomyocytes. For autophagy in CVD, the publication output was greater than that of the other types of cell death. The increase in the overall number of publications was particularly high in 2021 and 2022, indicating the high degree of interest in this field.

China ranked first in the number of articles published in this field. In the field of necroptosis in CVD, except for Comenius University Bratislava in Slovakia, the most prolific institutions were all from China, including Harbin Medical University, Zhejiang University, and

Table 5 The top 10 co-cited references in the field of necroptosis, pyroptosis, ferroptosis, and autophagy in cardiovascular disease

Type	Rank	Reference	Co-citations	Year
Necroptosis	1	Zhang T, 2016, *Nat Med*, V22, p175, doi: 10.1038/nm.4017 (24)	117	2016
	2	Luedde M, 2014, *Cardiovasc Res*, V103, p206, doi: 10.1093/cvr/cvu146 (30)	81	2014
	3	Sun L, 2012, *Cell*, V148, p213, doi: 10.1016/j.cell.2011.11.031 (58)	76	2012
	4	Cho Y, 2009, *Cell*, V137, p1112, doi: 10.1016/j.cell.2009.05.037 (59)	75	2009
	5	Degterev A, 2005, *Nat Chem Biol*, V1, p112, doi: 10.1038/nchembio711 (60)	72	2005
	6	He S, 2009, *Cell*, V137, p1100, doi: 10.1016/j.cell.2009.05.021 (61)	68	2009
	7	Oerlemans MI, 2012, *Basic Res Cardiol*, V107, doi: 10.1007/s00395-012-0270-8 (62)	64	2012
	8	Zhang DW, 2009, *Science*, V325, p332, doi: 10.1126/science.1172308 (63)	63	2009
	9	Degterev A, 2008, *Nat Chem Biol*, V4, p313, doi: 10.1038/nchembio.83 (64)	61	2008
	10	Wang H, 2014, *Mol Cell*, V54, p133, doi: 10.1016/j.molcel.2014.03.003 (65)	57	2014
Pyroptosis	1	Shi J, 2015, *Nature*, V526, p660, doi: 10.1038/nature15514 (66)	130	2015
	2	Shi J, 2017, *Trends Biochem Sci*, V42, p245, doi: 10.1016/j.tibs.2016.10.004 (67)	107	2017
	3	Liu X, 2016, *Nature*, V535, p153, doi: 10.1038/nature18629 (68)	99	2016
	4	Bergsbaken T, 2009, *Nat Rev Microbiol*, V7, p99, doi: 10.1038/nrmicro2070 (25)	85	2009
	5	Kayagaki N, 2015, *Nature*, V526, p666, doi: 10.1038/nature15541 (69)	72	2015
	6	Zhaolin Z, 2019, *Cell Proliferat*, V52, doi: 10.1111/cpr.12563 (16)	71	2019
	7	Duewell P, 2010, *Nature*, V464, p1357, doi: 10.1038/nature08938 (70)	69	2010
	8	Ding J, 2016, *Nature*, V535, p111, doi: 10.1038/nature18590 (71)	60	2016
	9	Wu X, 2018, Cell Death Dis, V9, doi: 10.1038/s41419-017-0257-3 (37)	57	2018
	10	Kawaguchi M, 2011, Circulation, V123, p594, doi: 10.1161/circulationaha.110.982777 (72)	54	2011
Ferroptosis	1	Dixon SJ, 2012, Cell, V149, p1060, doi: 10.1016/j.cell.2012.03.042 (73)	390	2012
	2	Fang X, 2019, *Proc Natl Acad Sci U S A*, V116, p2672, doi: 10.1073/pnas.1821022116 (26)	276	2019
	3	Stockwell BR, 2017, *Cell*, V171, p273, doi: 10.1016/j.cell.2017.09.021 (74)	197	2017
	4	Yang WS, 2014, *Cell*, V156, p317, doi: 10.1016/j.cell.2013.12.010 (75)	192	2014
	5	Friedmann Angeli JP, 2014, *Nat Cell Biol*, V16, p1180, doi: 10.1038/ncb3064 (76)	155	2014
	6	Gao M, 2015, *Mol Cell*, V59, p298, doi: 10.1016/j.molcel.2015.06.011 (43)	148	2015
	7	Doll S, 2017, *Nat Chem Biol*, V13, p91, doi: 10.1038/nchembio.2239 10.1038/nchembio.2239 (77)	129	2017
	8	Xie Y, 2016, *Cell Death Differ*, V23, p369, doi: 10.1038/cdd.2015.158 (42)	121	2016
	9	Fang X, 2020, *Circ Res*, V127, p486, doi: 10.1161/circresaha.120.316509 (45)	113	2020
	10	Baba Y, 2018, *Am J Physiol-Heart C*, V314, ph659, doi: 10.1152/ajpheart.00452.2017 (2)	106	2018
Autophagy	1	Nakai A, 2007, *Nat Med*, V13, p619, doi: 10.1038/nm1574 (78)	683	2007
	2	Matsui Y, 2007, *Circ Res*, V100, p914, doi: 10.1161/01.res.0000261924.76669.36 (79)	680	2007
	3	Zhu H, 2007, *J Clin Invest*, V117, p1782, doi: 10.1172/jci27523 (80)	388	2007
	4	Levine B, 2008, *Cell*, V132, p27, doi: 10.1016/j.cell.2007.12.018 (81)	377	2008
	5	Kim J, 2011, *Nat Cell Biol*, V13, p132, doi: 10.1038/ncb2152 (82)	373	2011
	6	Mizushima N, 2008, *Nature*, V451, p1069, doi: 10.1038/nature06639 (83)	287	2008
	7	Yan L, 2005, *Proc Natl Acad Sci U S A*, V102, p13807, doi: 10.1073/pnas.0506843102 (84)	256	2005
	8	Mizushima N, 2011, *Cell*, V147, p728, doi: 10.1016/j.cell.2011.10.026 (85)	254	2011
	9	Hamacher-Brady A, 2006, *J Biol Chem*, V281, p29776, doi: 10.1074/jbc.m603783200 (86)	232	2006
	10	Ma X, 2012, *Circulation*, V125, p3170, doi: 10.1161/circulationaha.111.041814 (52)	228	2012

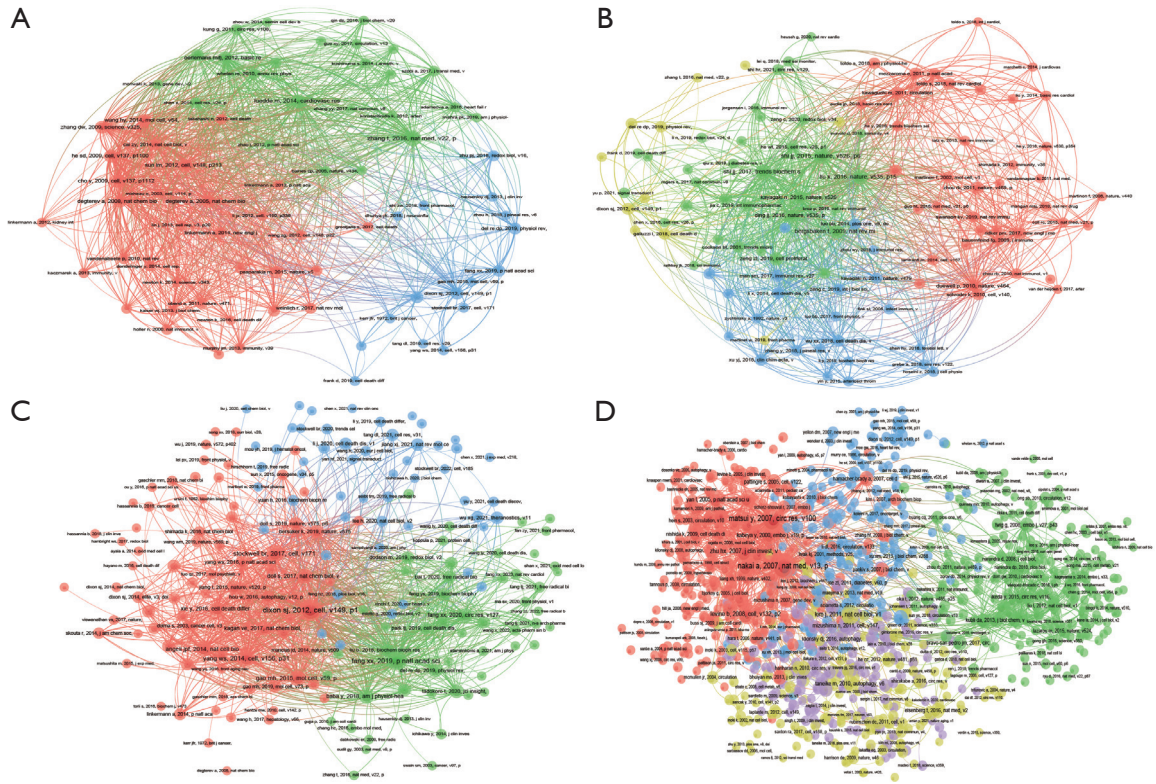

Figure 8 VOSviewer visualization map of the co-citation analysis for articles. (A) Necroptosis in cardiovascular disease. (B) Pyroptosis in cardiovascular disease. (C) Ferroptosis in cardiovascular disease. (D) Autophagy in cardiovascular disease.

Fudan University; this indicates that Chinese institutions have shown a growing interest in investigating the role of programmed cell death (PCD) in CVD. As shown in Figures S1-S3, cooperation among countries/regions, as demonstrated via co-authorship, citation, and bibliographic coupling analyses, was observed between China and the United States, with limited cooperation between other nations. As shown in Figures S4-S6, certain institutions were particularly isolated, including Stellenbosch University, the University of Monastir, Kyungpook National University, Ewha Womans University, and the Indian Institute of Technology Kanpur, indicating a lack of collaboration for these organizations. It is strongly recommended that communication between institutions intensifies to facilitate advancements in the fields of autophagy, ferroptosis, necroptosis, and pyroptosis in CVD.

The top 10 most-published authors and co-cited authors in the field of necroptosis in CVD are listed in *Table 2* and Figures S2-S5, among whom Adameova A published 22 articles, ranking first in the field of necroptosis in CVD. In the field of pyroptosis in CVD, Ge J and Ye B published each 8 articles, ranking fist in this field, and were followed by Dai S (7 articles). However, the number of citations for Ge J (239 citations) was higher than that for Ye B (211 articles). The leading researcher in the field of autophagy and ferroptosis in CVD was Ren J, with 10 and 120 articles, respectively. In the field of ferroptosis, the number of published papers by Matsui T was less than that of Ren J, but Matsui T was cited more (463 citations) as compared to Ren J (204 citations).

In and co-citation analysis of journals was found that over 50% of the top 10 journals in number of co-citations were the Q1 and Q2 journals (*Table 3* and Figure S9, *Figure 4*). Journal co-citation analysis has also indicated that the top two most-cited journals were *Cell* and *Nature* in the fields of ferroptosis in CVD, necroptosis in CVD, and pyroptosis in CVD, respectively, each with over 500 citations. Slightly different from these fields, in the field of autophagy in CVD, the *Journal of Biological Chemistry* (12,012 citations) was the most frequently cited journal, followed by *Circulation Research* (11,966 citations) (*Table 3* and *Figure 5*). In summary, the fields of autophagy,

ferroptosis, necroptosis, and pyroptosis in CVD are all research hotspots that appear to be growing. Additionally, the cited literature from high-impact journals indicates that these research areas are highly regarded in the academic community.

Based on the data of top 10 co-cited references in the field of necroptosis, pyroptosis, ferroptosis, and autophagy in CVD, the article "CaMKII is a RIP3 substrate mediating ischemia- and oxidative stress-induced myocardial necroptosis" was the most cited article (514 citations) in necroptosis in CVD (24); in pyroptosis in CVD, "Pyroptosis: host cell death and inflammation" was the most cited (2,105 citations) (25); in ferroptosis in CVD, "Ferroptosis: process and function" was the most cited (1,959 citations) (42); and in the field of autophagy in CVD, "Cardioprotection and lifespan extension by the natural polyamine spermidine" was the most cited (681 citations) (27). All the articles related to necroptosis, pyroptosis, and autophagy in CVD were published in Q1 and Q2 journals, with those published on ferroptosis being the exception. The different types of cell death in CVD are at the frontiers of CVD research.

The research hotspots for necroptosis in CVD

Necroptosis, a form of programmed necrosis, was first identified by Degterev *et al.* in 2005 as a tumor necrosis factor receptor-mediated process that can be inhibited by necrostatin-1 (Nec-1), a small-molecule inhibitor of RIPK1 (60). Once TNF-α binds to tumor necrosis factor receptor I (TNFRI), it will recruit TNFR1-associated death domain protein (TRADD). Subsequently, TRADD recruits RIPK1 through DD-DD interaction. It forms the membrane-bound complex I, which is composed by TRADD, TNFR-associated factor 2, TNFR-associated factor 5, RIP1, and cellular inhibitor of apoptosis 1/2 (22). The conversion of complex I to complex II is dependent on the de-ubiquitination of RIP1 (28). De-ubiquitination of RIP1 promotes the autophosphorylation of RIP1 (Ser161), which subsequently enhances the phosphorylation of RIP3 (Ser227 in humans and Thr231/Ser232 in mice) to activate MLKL protein (Thr357 and Ser358 in humans and Ser358 in mice), forming pores and leading to cell death.

Recent studies have confirmed the detrimental role of necroptosis in MIRI. For instance, RIP3-deficient mice exhibit significantly reduced myocardial inflammation and hypertrophy following MIRI, along with improved cardiac function, including enhanced ejection fraction (24,30). These findings underscore the importance of RIP3 in driving necroptosis-mediated cardiac injury. Supporting this, Zhu *et al.* reported that RIP3 triggers endoplasmic reticulum (ER) stress, which is associated with elevated intracellular Ca^{2+} levels [$(Ca^{2+})c$] and increased xanthine oxidase (XO) expression. The activation of XO in turn leads to higher levels of cellular reactive oxygen species (ROS), which mediates the opening of the mitochondrial permeability transition pore (mPTP) and induces necroptosis in cardiomyocytes (29). This mechanistic link between RIP3 and mitochondrial dysfunction provides an important avenue for therapeutic intervention.

In addition to the RIP1/RIP3/MLKL pathway, calcium/calmodulin-dependent protein kinase II (CamKII), another RIP3 substrate, triggers opening of the mPTP and myocardial necroptosis, according to a study by Zhang *et al.* group (24). Furthermore, hesperadin, a CamKII-δ inhibitor, has been found to ameliorate myocardial I/R injury (88). In addition to examining different signaling pathways related to necroptosis, research has focused on the inhibition of necroptosis to improve cardiac protection.

Growing evidence suggests that simultaneous inhibition of necroptosis and apoptosis offers synergistic protection against myocardial I/R injury. It has been suggested that a combination of necroptosis and apoptosis inhibition can enhance cardioprotection against myocardial I/R injury (32). Interestingly, another study found that TNF-α-associated factor 2 can protect cardiomyocytes from both apoptosis and necroptosis in those with heart failure (34), which could represent a novel therapeutic target for addressing pathological remodeling and heart failure. The most promising strategies in the death receptor pathway include inhibiting RIPK1 and RIPK3, with RIPK3 potentially providing greater benefit due to its broader range of downstream targets. Necrostatin-1 was the first inhibitor of necroptosis to be identified (60). However, a study has found that necrostatin-1 is not a selective inhibitor of necroptosis due to possessing multiple targets, including indoleamine 2,3-dioxygenase (IDO) (89). Therefore, several possible targets for inhibiting necroptosis may be available, including necrostatin-1 stable (a selective inhibitor of RIP1), GSK'074 (an inhibitor of RIP1 ad RIP3) (90), and necrosulfonamide (a molecule that inactivates necrosomes) (58). However, due to the insoluble nature of GSK'074 and necrosulfonamide, further in depth research is ongoing.

The research hotspots for pyroptosis in CVD

The term "pyroptosis", first proposed by Cookson and

Brennan, combines the Greek words *pyro* (meaning fire or fever) and *ptosis* (meaning falling). It describes a type of inflammatory PCT that was first observed in macrophages. Pyroptosis was initially characterized as relying on caspase-1 and GSDMD. In this process, microorganism- and host-derived "danger" signals trigger the formation of a multiprotein complex known as the inflammasome, which results in the processing and activation of caspase-1 (25,91). Mezzaroma *et al.* reported that the formation of the inflammasome that includes an apoptosis speck-like protein containing a caspase-recruitment domain (ASC), cryopyrin, and caspase-1, in the mouse heart during acute myocardial infarction (AMI) results in additional loss of the functional myocardium, leading to heart failure. In their study, blocking P2X7 and cryopyrin (using RNA silencing or a pharmacological inhibitors) prevented the inflammasome from forming and decreased infarct size and cardiac enlargement following AMI (36). Moreover, the production of ROS is an upstream mechanism involved in the activation of the NLRP3 inflammasome. Studies have found that nicotine-induced ROS production and oxidative stress are likely upstream mechanisms driving the activation of the NLRP3 inflammasome, a process that can be counteracted by N-acetyl-cysteine (NAC), a ROS inhibitor (16,37,92).

Another target that can initialize pyroptosis is GSDMD. The activated form of GSDMD, comprising an N-terminal domain, has the capability to aggregate and create pores within the cell membrane, which causes the membrane to disrupt, potentially triggering cell death, while also facilitating the release of inflammatory agents such as interleukin (IL)-1β and IL-18. Previous studies have found that the pyroptosis of vascular smooth muscle cells (VSMCs) leads to unstable atherosclerotic plaques and acute coronary syndrome, while the pyroptosis of monocytes and macrophages intensifies inflammation and drives the development of various CVDs (28,38,40,41). However, in 2021, Shi *et al.* proposed that during myocardial I/R injury, the principal occurrence was cardiomyocyte pyroptosis facilitated by GSDMD and that the inhibition of GSDMD can reduce cardiomyocyte pyroptosis in this process (21,87).

Cleavage of GSDME by caspase-3 can trigger pyroptosis in some cancer cells following chemotherapy, a phenomenon known as noncanonical pyroptosis. In 2020, Zheng *et al.* reported that doxorubicin (DOX)-induced cardiomyocyte pyroptosis is mediated by GSDME and activated by the upregulation of Bnip3 and cleaved caspase-3 (93). Their findings indicate that targeting pyroptosis could be effective in reducing DOX-induced cardiomyocyte injury.

The research hotspots for ferroptosis in CVD

As a form of regulated cell death, ferroptosis is mediated by the iron-dependent accumulation of lipid hydroperoxides. Iron functions as a cofactor in heme and iron-sulfur cluster-containing proteins that regulate essential processes, such as oxygen transport and oxidative phosphorylation (42). Mice that lack ferritin heavy chain (FTH) specifically in either myocytes or cardiomyocytes exhibit altered cardiac iron homeostasis and develop mild cardiomyopathy at young age. These mice having reduced cardiac iron levels and dietary iron supplementation are affected by severe left ventricular hypertrophy and heart injury due to ferroptosis. This damage can be mitigated either by overexpressing Slc7a11 or administering the ferroptosis inhibitor ferrostatin-1 to the mice (45).

Notably, cystine/glutamate antiporter (System Xc^-), GPX4, and glutathione (GSH) (collectively referred to as the system Xc^-GSH^-GPX4 axis) are crucial to prevent the lipid peroxidation-induced ferroptosis (15). Fang *et al.*'s group found that iron-dependent ferroptosis was a greater contributor to DOX-induced cardiomyopathy than were other known forms of regulated cell death. Moreover, they found that the activation of Nrf2 leads to the upregulation of Hmox1, resulting in heme degradation in the heart. This process releases free iron, which accumulates in the mitochondria and causes lipid peroxidation (26). A variety of inhibitors and promoters related to ferroptosis have been identified thus far. Liu *et al.* reported that puerarin, one of the most abundant phytoestrogens with antioxidant and other properties, exerts protective effects against cardiomyocyte hypertrophy through ferroptosis mitigation in rats (48). Transferrin transport and the cellular metabolic process of glutaminolysis are crucial for the ferroptosis induced by the lack of all amino acids or cystine alone. In another study, it was demonstrated that targeting glutaminolysis could be an effective therapeutic strategy for treating heart injury resulting from I/R injury (43). Other research indicates that mammalian target of rapamycin (mTOR) is essential and sufficient to prevent iron-mediated cell death (2). The overexpression of mTOR prevents cell death resulting from excess of iron and ferroptosis, while the absence of mTOR amplifies cell death induced by excessive iron and ferroptosis in cardiomyocytes.

Doll *et al.* and Bersuker *et al.* identified that FSP1, in addition to the canonical GSH-based GPX4 pathway, is a

crucial part of a non-mitochondrial CoQ antioxidant system that regulates phospholipid peroxidation and ferroptosis (94,95). Meanwhile, Qiu *et al.*'s group reported that idebenone, a novel ferroptosis inhibitor, stabilizes FSP1 protein levels by inhibiting its ubiquitination degradation, resulting in the attenuation of DOX-induced cardiotoxicity (96). Untargeted metabolomic analysis identified dihydroorotate dehydrogenase-coenzyme Q (DHODH-CoQ) as another crucial anti-ferroptotic pathway (97). Zhu *et al.* found that the suppression of Cirbp expression, due to aging, weakens the cardioprotective effects of hypothermia by diminishing DHODH-mediated ferroptosis defense, leading to increased ferroptosis in aged donor hearts after transplantation (98).

The research hotspot for autophagy in CVD

Autophagy, derived from the Greek words *auto* (oneself) and *phagy* (to eat), describes any cellular degradation pathway that transports cytoplasmic material to the lysosome (57,99). Autophagy is an intracellular process responsible for the bulk degradation of proteins and organelles. The role of autophagy varies significantly across different stages of disease progression and among different cell types (10). In the cardiomyocytes, autophagy is triggered by myocardial ischemia. Autophagy can be divided into different types including chaperone-mediated autophagy, microautophagy, and macroautophagy (49,55). Hamacher-Brady *et al.* examined the role of macroautophagy in myocardial ischemia reperfusion injury and found that autophagic flux is disrupted at both the initiation and degradation stages; they thus concluded that enhancing autophagy represents a potent and—at that time—previously unrecognized protective mechanism against I/R injury in heart cells (86). Eisenberg *et al.* reported that spermidine feeding might enhance cardiac autophagy, mitophagy, and prevent cardiac hypertrophy via Atg5 (27). However, a different study found that in different processes of myocardial I/R, the role of autophagy varies. Autophagy may exert a protective effect during ischemia, but it can be detrimental during reperfusion (79). Additionally, Ma *et al.* reported that re-oxygenation caused more death in neonatal rat cardiomyocytes than did hypoxia alone and significantly increased the number of autophagosomes but not autolysosomes (52). Impaired autophagosome homeostasis can be influenced by ROS, which leads to a decrease of LAMP2 and an increase of BECLIN-1, resulting in a greater degree of cardiomyocyte death.

In addition, several mitochondria-related proteins have been investigated in their relation to autophagy. Recent discoveries have highlighted the significant role of the E3 ubiquitin ligase Parkin in marking damaged mitochondria for removal through the process of autophagy. Kubli *et al.* found that Parkin-knockout mice exhibited reduced survival and developed larger infarcts compared to wild-type mice following infarction. Notably, in wild-type mice, the expression of Parkin and mitochondrial autophagy (mitophagy) rapidly increased in the border zone of the infarct (53). Dynamin-related protein 1 (Drp1) regulates mitochondrial fission sites. One study found that Drp1 physically interacts with Bcl-2/Bcl-xL and that the downregulation of Drp1 enhances the interaction between Beclin1 and Bcl-2/Bcl-xL, which in turn leads to the suppression of autophagy and exacerbates myocardial injury in response to I/R (50).

Future outlook

While preclinical advances have shed light on the importance of PCD in CVD, overcoming these translational barriers will be crucial to unlocking their therapeutic potential. A major limitation is the lack of specific and safe pharmacological modulators for each PCD pathway. For example, while necrostatins (e.g., necrostatin-1) are widely used to inhibit RIPK1-mediated necroptosis in preclinical studies, their off-target effects and limited pharmacokinetics have hindered clinical development (100). Similarly, although ferroptosis inhibitors like ferrostatin-1 and liproxstatin-1 show promise in animal models, none have advanced to clinical trials in cardiovascular settings (92). Only through further optimization and rigorous testing of these compounds will we be able to conduct meaningful human studies to answer the question of whether the inhibition of ferroptosis, apoptosis, or other forms of cell death in CVD will translate into clinical benefit.

Limitation

Our study is the first study to employ a bibliometric analysis in the fields of necroptosis in CVD, pyroptosis in CVD, ferroptosis in CVD, and autophagy in CVD, yet several limitations should be noted. First, the literature we reviewed was published from January 1, 2009 to December 31, 2023. However, since the WoSCC is continually updated, our search results may differ from the current number of relevant publications. Second, the analysis

was solely based on the WoSCC, and relevant studies indexed in other databases or within the grey literature might have been missed, potentially introducing selection bias. Third, as bibliometric analysis is addressed based on keyword extraction, the results might have been affected by the incomplete extraction of keywords. Lastly, although we recognized interdisciplinary collaboration as a key driver of progress in this field, our current analysis did not delve deeply into the nature of existing collaborations across disciplines such as cardiology, molecular biology, and computational sciences—an area that deserves further investigation in future studies. Nonetheless, our analysis could effectively capture the trends, countries/regions, institutions, journals, authors, and co-citations of publications on autophagy, ferroptosis, necroptosis, pyroptosis in the context of CVD.

Conclusions

Our study provides a bibliometric analysis of the literature on autophagy, ferroptosis, necroptosis, and pyroptosis in the context of CVD, examining the authors, institutions, countries/regions, and high-quality publications. Our findings suggest that we should strengthen communication between difference institutions in the future. The bulk of research in this field has focused on the pathways, crosstalk, and inhibitors of the different types of PCD in CVD. Further examination of different cell death processes through clinical trials is warranted.

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Footnote

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