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Research Hotspots and Trends in Diabetic Vascular Calcification: A Bibliometric and Visualization Analysis

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Abstract: Diabetic vascular calcification (DVC) is a significant manifestation of vascular complications in diabetes, markedly increasing the risk of cardiovascular events and affecting the long-term prognosis of diabetic patients. This study aims to provide a comprehensive and visual perspective on DVC research, laying the foundation for further investigations. Relevant literature on DVC was retrieved from the Web of Science Core Collection (WoSCC) database. Bibliometric and visualization analyses of the DVC research field were conducted using CiteSpace 6.3.R1 software, focusing on aspects such as countries/regions, institutions, authors, journals, references, and keywords. A total of 1,864 articles on DVC were identified, including 1,521 research papers and 343 reviews. These publications involved 71 countries/regions, 813 institutions, and 10,064 authors. The articles were distributed across 590 journals, with 1,107 references cited more than ten times. The most prolific author was John Jeffrey Carr, with 26 publications. The University of California system was the most productive institution, with 104 papers. The United States led with 506 papers, and Nephrology Dialysis Transplantation was the most frequently published journal, with 57 papers. The most highly cited article, published by Shuichi Jono in 2000 in Circulation Research has been cited 1,164 times. The most co-cited reference was published by Andrew L. Durham in 2018 in Cardiovascular Research with 42 co-citations. The top five keyword clusters were ‘peripheral arterial disease’, ‘fibroblast growth factor 23’, ‘bone mineral density’, ‘diabetes mellitus’ and ‘chronic kidney disease’. The most frequently cited keyword was ‘vascular calcification’. This study analyzed the research hotspots, frontiers, and development trends in DVC. The research on DVC is evolving towards a comprehensive, personalized, and precision medicine approach. Global participation should be encouraged to enrich scientific perspectives and drive scientific and clinical innovation.

1. Introduction

Diabetes and its complications have become a global health challenge, posing a significant burden on public health systems. According to statistics from the International Diabetes Federation (IDF), the estimated prevalence of diabetes among the global population aged 20 to 79 in 2021 is

10.5%, affecting approximately 536.6 million people. It is projected that by 2045, this rate will rise to 12.2%, affecting about 783.2 million people[1]. Diabetic vascular calcification (DVC) is one of the common vascular complications in diabetic patients. It can be categorized into intimal and medial calcification based on the location of occurrence[2]. Pathologically, it is the deposition of hydroxyapatite minerals within the vascular system. This pathological change significantly increases the risk of cardiovascular events[3]. Epidemiological data indicate that the incidence of medial vascular calcification in diabetic patients is markedly higher than in non-diabetic individuals[4], and it is more pronounced in patients with diabetic peripheral vascular disease[5]. A cross-section study indicate that as the duration of diabetes increases, the proportion of diabetic patients showing signs of vascular calcification tends to rise[6].

Diabetes is an independent risk factor for vascular calcification, and its occurrence and development may be influenced by multiple factors, including aging, hypertension, osteoporosis, and chronic kidney disease (CKD)[7]. Under the stimulation of hyperglycemia and other factors, endothelial cells activate bone morphogenetic signaling pathways through endothelial-to-mesenchymal transition (EndMT), releasing cytokines and matrix vesicles that promote the differentiation of vascular smooth muscle cells (VSMCs) into bone-like cells. These cells can transition from a contractile to a proliferative phenotype and migrate to the intima, facilitating the formation of extracellular matrix and serving as a primary source of calcification vesicles[8]. Currently, there are no reversal treatments for DVC, and therapeutic strategies primarily focus on inhibiting or alleviating the progression of DVC. This includes strict control of blood glucose levels and blood pressure, as well as using hypoglycemic and antihypertensive medications to reduce the risk of vascular calcification[9,10]. Additionally, anti-calcification drugs such as vitamin K1 and its derivatives show promise in slowing down the progression of calcification by regulating the function of calcification-inhibiting proteins[11].

In recent years, significant research findings on DVC have emerged, and research in this area continues to deepen. Currently, researchers worldwide have published numerous preclinical and clinical studies on DVC. However, a comprehensive review of the overall distribution of these publications remains relatively insufficient. Bibliometrics is a discipline focused on the quantitative analysis of scientific literature, using statistical and mathematical models to analyze and interpret the distribution, citation patterns, and author productivity of scientific literature, in order to reveal the patterns of scientific activity, assess research impact, and predict development trends[12]. This study employs bibliometric analysis to conduct a comprehensive analysis of the literature on DVC over the past 20 years, aiming to reveal research hotspots and development trends in this field and to provide researchers with a comprehensive perspective to promote a deeper understanding and future exploration of DVC.

2. Materials and methods

2.1. Data Source and Search Strategy

The Web of Science Core Collection is a comprehensive academic information resource covering multiple disciplines. To ensure data quality and availability, all data were downloaded from the Web of Science Core Collection online database. The search strategy was as follows: TS=("diabete*" OR "diabetic*" OR "diabetic mellitus") AND TS=("vascular calcification" OR "arterial calcification" OR "aortic calcification" OR "vascular smooth muscle cell mineralization" OR "vascular smooth muscle cell calcification"). The time range was set from January 1, 2000, to June 30, 2024, yielding a total of 2,012 articles. The search was restricted to articles and review papers, and the language was limited to English, resulting in a final collection of 1,864 articles. These articles were selected for full-text review and citation analysis, and then exported in txt

format. A detailed flowchart of the process is presented in Figure 1.

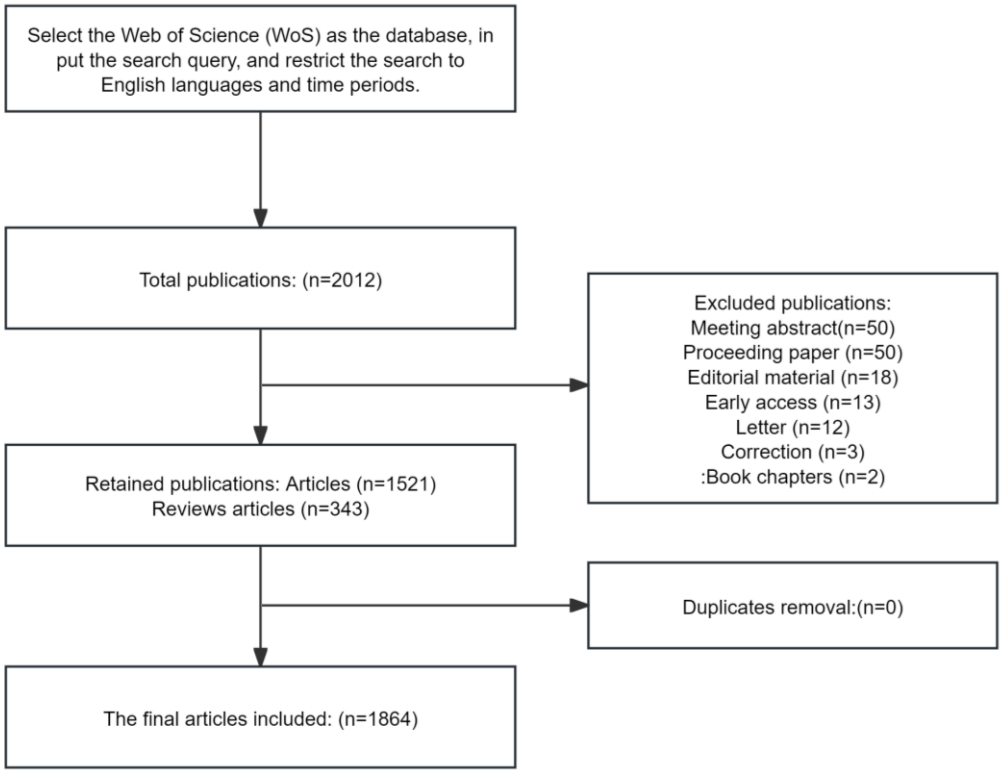

Figure 1: Inclusion and exclusion criteria flowchart.

2.2. Analysis Methods

CiteSpace 6.3.R1 was utilized as a bibliometric analysis tool to perform quantitative analysis on various aspects of DVC research, including countries, institutions, authors, journals, keywords, and references. Journal Citation Reports (JCR) and H-index were also used to assist in evaluating the academic impact of journals. CiteSpace, developed by Professor Chaomei Chen from Drexel University, is a document visualization analysis tool focused on bibliometric analysis and data visualization[13]. The software is interactive, allowing users to explore nodes and connections within a network through clicking and dragging. CiteSpace also provides quantitative analysis tools such as node centrality to help identify key nodes. Additionally, it features advanced functions like clustering analysis, burst detection, and timeline analysis to aid researchers in understanding the hotspots and trends within the research field. Furthermore, Microsoft Word 2019 was used to create annual publication trend graphs. ArcGIS 10.8 was employed to generate geographic distribution maps of publications. Scimago Graphica 1.0.36 was used to draw annual publication trend graphs by country.

2.3. Statistical Methods

In this study, all tabular data were sourced from the analysis results and citation reports of the Web of Science Core Collection (WoSCC). Bibliometric analysis was conducted using CiteSpace 6.3.R1, which provided centrality analysis to help identify key nodes acting as bridges in the research network. To more accurately model data trends, polynomial curve fitting analysis was employed. Polynomial fitting is a powerful statistical technique that estimates the value of a dependent variable by constructing polynomial equations involving one or more independent

variables. The goal of this model is to make the predicted values as close as possible to the observed data points, thereby revealing the underlying relationships and trends between variables[14]. Cluster analysis is conducted using the Log-Likelihood Ratio (LLR) algorithm provided by CiteSpace. This algorithm is a feature selection method for text classification systems based on the Vector Space Model. It effectively considers the positive impact of rare events on classification outcomes while controlling their potential negative effects[15].

3. Results and Analysis

3.1. Publication Growth Trend

A total of 1,864 publications were retrieved from WoSCC covering the years 2000 to 2024. As shown in Figure 2, publications related to DVC have shown a continuous growth trend over the past 20 years. From 2000 to 2004, research in this field was in its early stages, with fewer than 30 articles published annually. Starting in 2005, the number of papers on DVC increased at a rate of approximately 30 articles per year. Notably, from 2010 onwards, the publication volume saw a significant rise, with an annual increase of about 70 articles. By 2020 and 2021, the annual publication volume reached 165 and 160 articles, respectively, indicating that research in this field has gradually gained widespread attention. Although there was a slight decrease in publications in 2023, the cumulative publication volume continues to rise, demonstrating that research on DVC is generally still advancing.

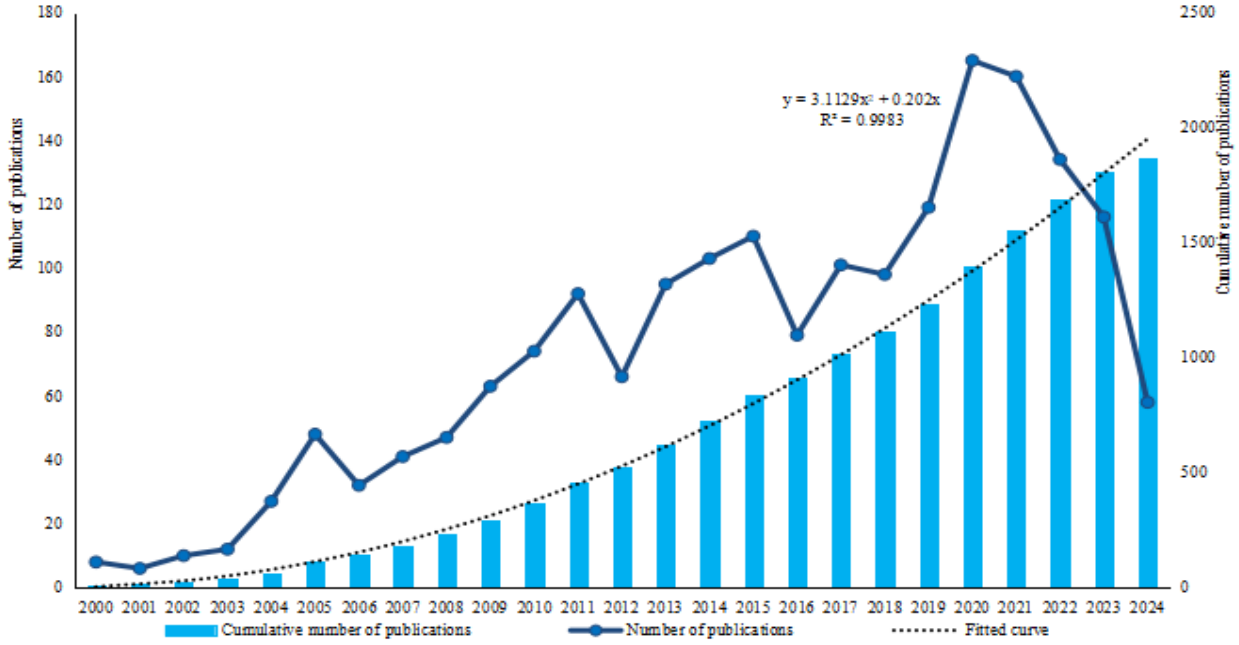

Figure 2: Trends in annual publication related to DVC.

3.2. Countries/Regions and Institutions Analysis

All publications came from 71 countries/regions. Figure 3A illustrates the geographical distribution of publications related to DVC research. Different shades of blue represent the number of articles published by each country. The leading country in terms of publication volume is the United States, with 506 publications (27.15%), followed by China (361 publications, 19.37%), Japan (162 publications, 8.69%), the United Kingdom (126 publications, 6.76%), and Germany (115 publications, 6.17%). These countries are dominant in DVC research. Publications from

Australia, South Korea, Italy, France, and Canada range between 52 and 91 articles. Overall, DVC research is primarily concentrated in developed countries and regions in North America, East Asia, and Western Europe. Table 1 summarizes the citation reports and H-index of the top ten productive countries. The top three countries with the highest average citation counts are Germany (68.47 citations), France (66.67 citations), and the United States (64.91 citations). The top three countries with the highest H-index are the United States (H-index 88), Germany (H-index 47), and the United Kingdom (H-index 42). Figure 3B displays the annual publication volume of the top ten countries/regions. The United States was the earliest to engage in DVC research and has published a significantly higher number of articles compared to other countries. China had a certain gap in publication volume compared to leading countries before 2010 but gradually increased its output from 2010 to 2018. After 2018, the annual publication volume in the United States declined, while China's annual output surpassed that of other countries, ranking first. Figure 3C depicts the collaboration relationships between countries/regions. Each circle represents a country, with the size indicating the number of publications from that country. Lines represent collaborative relationships between countries. Purple circles denote intermediary centrality, which measures the importance and influence of a node/country in the network. The United States, Germany, France, and Spain play key connecting roles in the global research collaboration network.

This study encompasses a total of 2,525 institutions. Table 2 summarizes the top ten productive institutions. The University of California System ranks first with 104 (5.58%) publications. Harvard University follows with 70 (3.76%) publications, and the US Department of Veterans Affairs ranks third with 56 (3.00%) publications. The top three institutions with the highest average citation counts are the University of Washington (122.29 citations), RWTH Aachen University (80.09 citations), and the University of California System (76.91 citations). The top three institutions with the highest H-index are the University of California System (H-index 41), Harvard University (H-index 30), and the US Department of Veterans Affairs (H-index 29), along with the University of Washington (H-index 29). Figure 3D shows the collaboration relationships between institutions. The University of California, San Francisco (UCSF) and Harvard University have the highest intermediary centrality, indicating their extensive collaboration networks in the field. Figure 3E displays the clustering of different research institutions within specific research topics, revealing the concentration and geographical distribution of academic research. The highly productive University of California System remains influential in research on phosphates, metabolomics, and advanced glycation end-products (RAGE) receptors, while Harvard University leads in obesity research.

Table 1: Top 10 countries/regions of productivity related to DVC

Rank	Country/Institution	Number of publications	% of 1864	Total times cited	Average citation frequency	H-index
1	United States	506	27.15	32907	64.91	88
2	China	361	19.37	6916	19.16	41
3	Japan	162	8.69	6736	41.58	40
4	United Kingdom	126	6.76	5993	48.33	42
5	Germany	115	6.17	7874	68.47	47
6	Italy	94	5.04	3763	40.03	32
7	South Korea	93	4.99	2352	25.29	24
8	Netherlands	89	4.77	4245	47.7	35
9	France	84	4.51	5600	66.67	38
10	Spain	78	4.18	2747	35.22	27

Table 2: Top 10 institutes of productivity related to DVC

Rank	Country/Institution	Number of publications	% of 1864	Total times cited	Average citation frequency	H-index
1	University Of California System	104	5.58	7999	76.91	41
2	Harvard University	70	3.76	4647	66.39	30
3	US Department of Veterans Affairs	56	3.00	3302	58.96	29
4	Institut National De La Sante Et De La Recherche Medicale Inserm	52	2.79	2902	55.81	27
5	Harvard Medical School	50	2.68	3052	61.04	25
6	University Of Washington	38	2.04	4647	122.29	29
7	Rwth Aachen University	33	1.77	2643	80.09	23
8	Wake Forest University	33	1.77	1172	35.52	18
9	Karolinska Institutet	32	1.72	2232	69.75	19
10	Maastricht University	32	1.72	2383	74.47	23

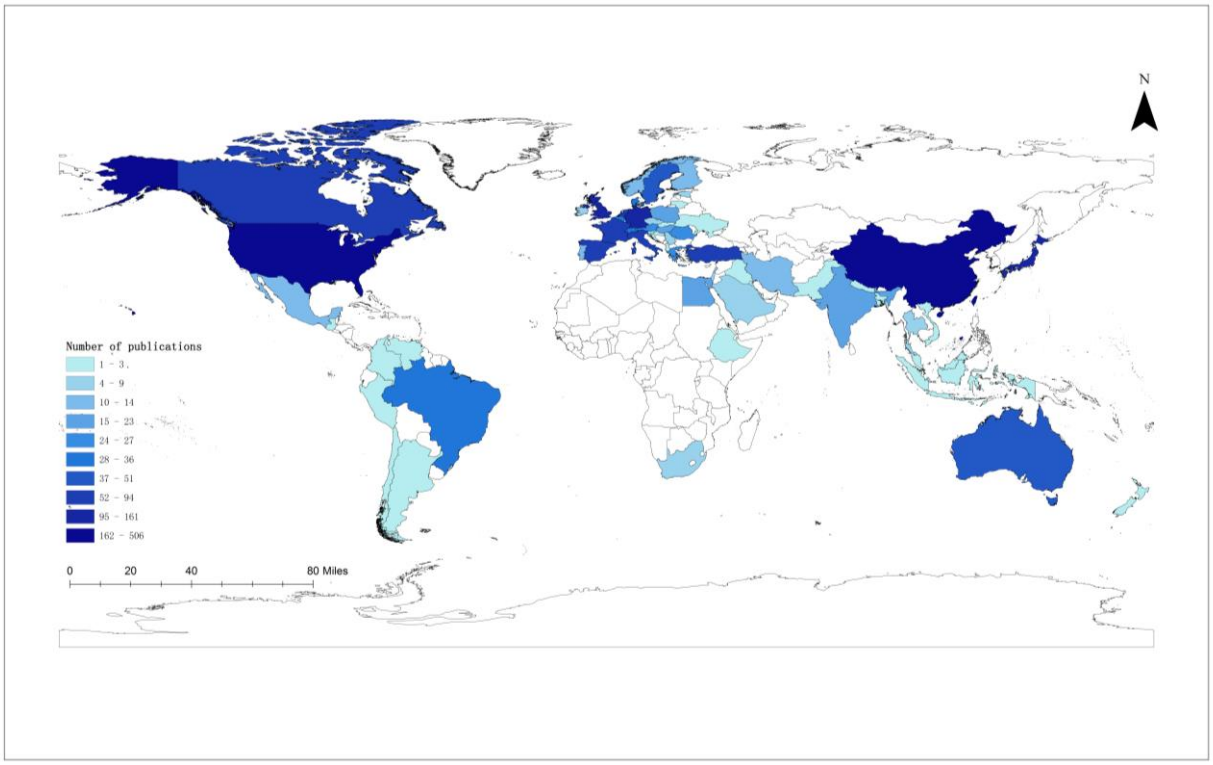

Figure 3A: Global geographic distribution map of publications

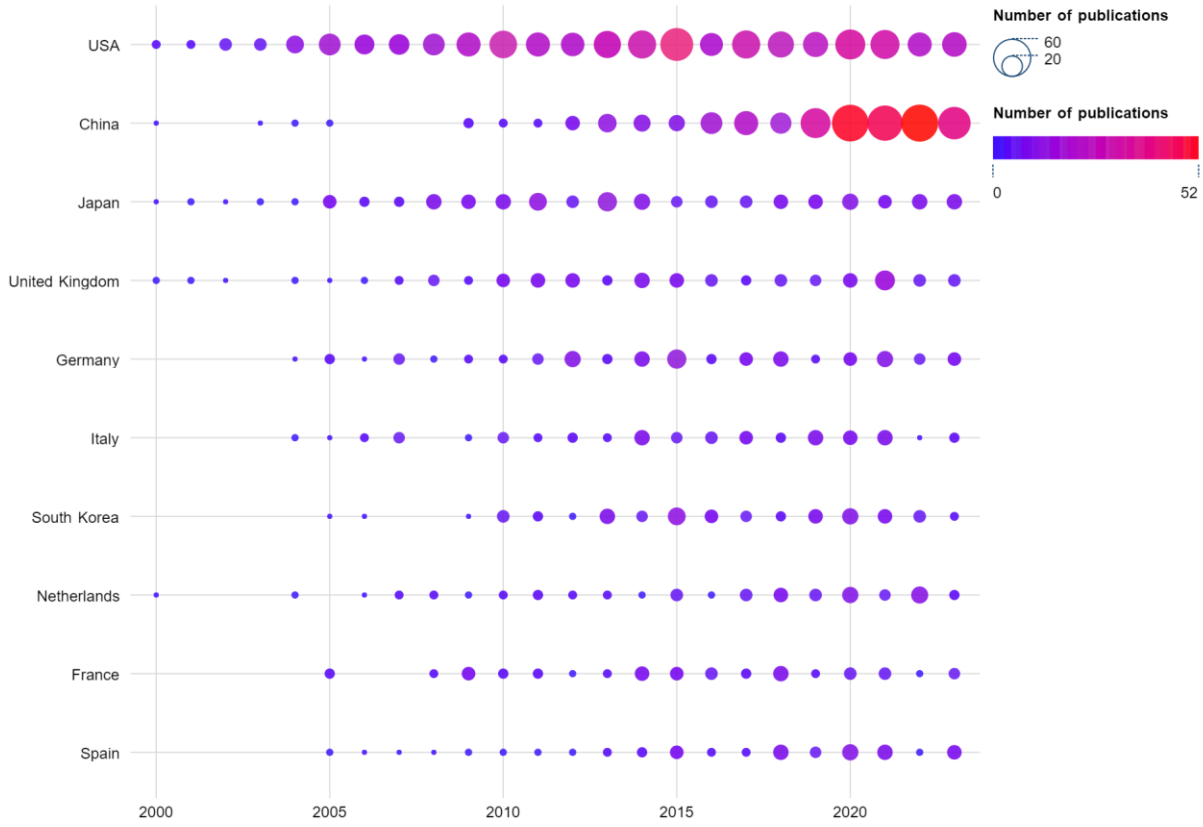

Figure 3B: Annual publication trends for the top ten countries/regions

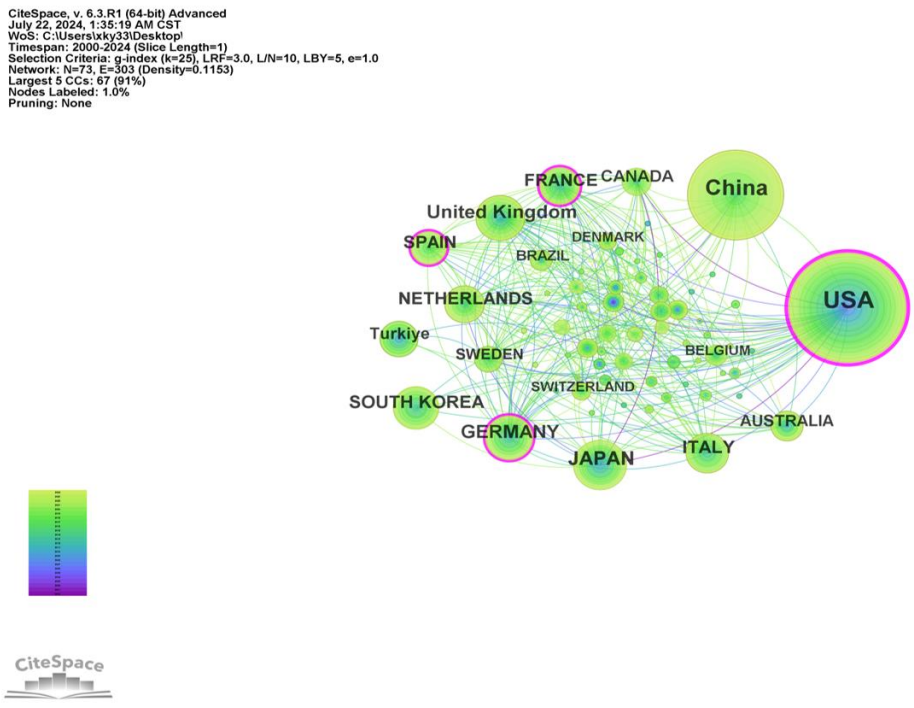

Figure 3C: Countries/regions collaboration map related to DVC

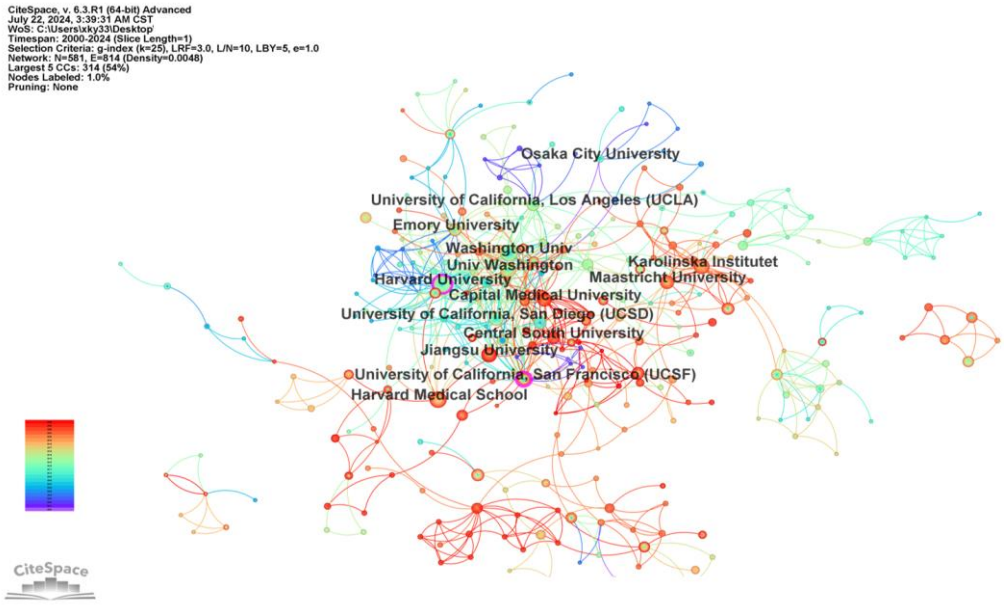

Figure 3D: Institutes collaboration map related to DVC

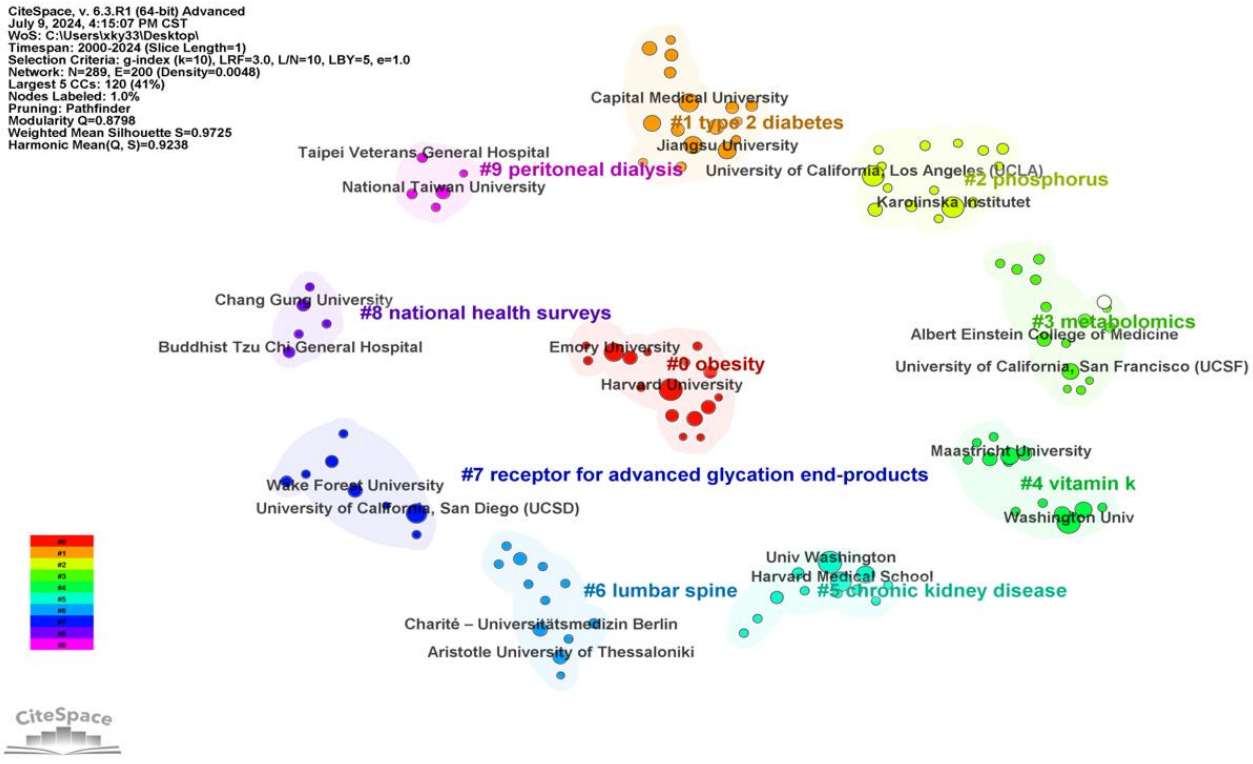

Figure 3E: Clustering map of collaborative institutions. The text with a "#" represents keyword clusters for the institutions

3.3. Author Analysis

A total of 10,064 researchers have contributed to DVC research. Table 3 presents the top 6 authors based on productivity and co-citation counts. In terms of author productivity, John Jeffrey Carr from Vanderbilt University School of Medicine leads with 26 published articles (H-index 16),

followed by Barry I. Freedman from Wake Forest University School of Medicine with 23 articles (H-index 14). Donald W. Bowden from Wake Forest University School of Medicine has published 22 articles (H-index 14). Dwight J. Fowler from UT Southwestern Medical Center has published 20 articles (H-index 20). Wang Zhongqun from Jiangsu University and Peter Stenvinkel from Karolinska Institute have both published 20 articles, with H-indexes of 10 and 13, respectively. In terms of citation metrics, Dwight J. Fowler stands out with a total of 1,849 citations and an average citation frequency of 123.27, far exceeding other authors.

Figure 4A illustrates the collaboration relationships among authors. Over the past decade, stable collaborations have been established between Donald W. Bowden, Barry I. Freedman, Carl D. Langefeld, and John Jeffrey Carr. In the past five years, Peter Barany, Bengt Lindholm, Abdul Rashid Qureshi, and Peter Stenvinkel have also formed collaborations. Additionally, Wang Zhongqun, Sun Zhen, and Li Hua have established their own collaboration networks. The author co-citation network reveals the influence and academic standing of these authors within their research field by showing the frequency of citations across different documents. Figure 4B displays the co-citation relationships among authors. Frequently cited figures such as Gerard Michel London from Manhès Hospital in France, Sharon M. Moe from Indiana University School of Medicine, and Paolo Raggi from the University of Alberta demonstrate their significant impact in the field.

Table 3: Top 6 authors of productivity and co-citation related to DVC

Rank	Author	Original country	Institute	Number of publications	Total times cited	Average citation frequency	H-index	Rank	Co-cited author	Original country	Institute
1	Carr, John Jeffery	United States	Vanderbilt University School of Medicine	26	688	26.46	16	1	London, Gerard Michel	France	French Clin Res Infrastruct Network Invest Network
2	Barry I. Freedman	United States	University of Washington	23	649	28.22	15	2	Moe, Sharon M.	United States	Indiana University System
3	Donald W. Bowden	United States	University of Washington	22	530	24.09	14	3	Raggi, Paolo	Canada	University of Alberta
4	Towler, Dwight A.	United States	University of Texas Southwestern Medical Center Dallas	20	1849	123.27	15	4	Jono, Shuichi	Japan	Osaka Metropolitan University
5	Wang, Zhongqun	China	Jiangsu University	20	300	15.79	9	5	Shanahan, Catherine M.	the United Kingdom	King's College London Faculty of Life Sciences & Medicine
6	Stenvinkel, Peter	Sweden	Karolinska Institutet	20	541	31.82	11	6	Linda L Demer	United States	University of California, Los Angeles

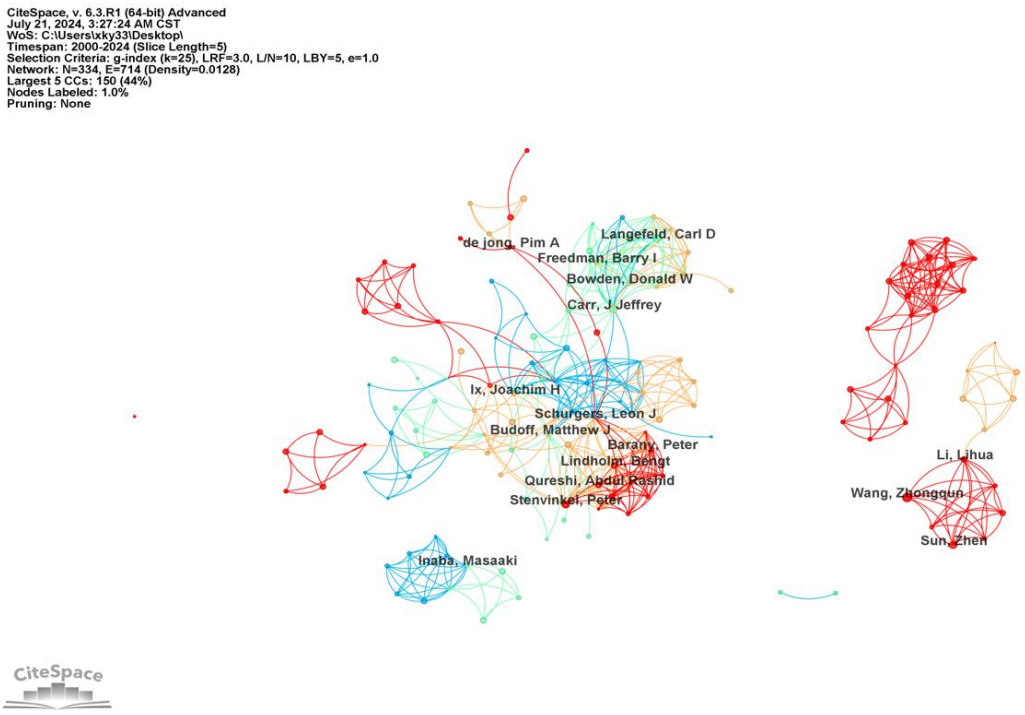

Figure 4A: Authors collaboration map related to DVC

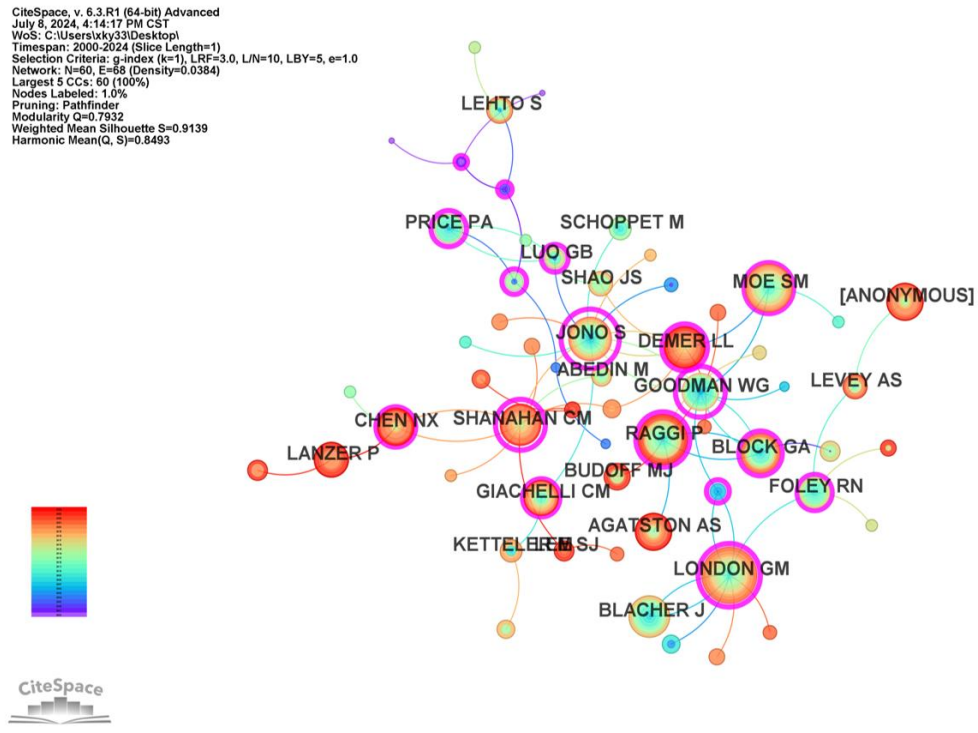

Figure 4B: Co-citation map of authors related to DVC

3.4. Journal Analysis

A total of 1,864 articles were published across 590 journals. Table 4 displays the top ten journals

based on publication productivity. In terms of journal productivity, *Nephrology Dialysis Transplantation* leads with 57 articles, accounting for 3.06% of the total publications. *Arteriosclerosis* ranks second with 50 publications, representing 2.68% of the total. Other notable journals include *International Journal of Molecular Sciences* (34 publications), *Public Library of Science One* (33 publications), and *Arteriosclerosis, Thrombosis, and Vascular Biology* (33 publications). These journals are typically classified as Q1 in the Journal Citation Reports (JCR), indicating their high academic impact within their respective fields.

Co-citation analysis of journals reveals the authoritative and influential journals in the field. Table 5 shows the top ten journals based on co-citation frequency. Among 5,268 co-cited journals, ten have been cited over 700 times, reflecting their authority and impact in the field. Of the 590 cited journals, ten have over 700 co-citations. *Circulation* is the most frequently co-cited journal with 1,290 co-citations and a centrality score of 1.03, indicating its core role in the field. It is followed by *Thrombosis and Haemostasis* with 1,063 co-citations and a centrality score of 0.96, and *Kidney International* with 1,003 co-citations and a centrality score of 0.49. Other highly co-cited journals include *Diabetes Care* (953 co-citations) and *Arteriosclerosis* (925 co-citations). Notably, all of the top ten most co-cited journals are classified as Q1 in the JCR. *The New England Journal of Medicine* has the highest impact factor (IF) of 96.2, followed by *Journal of the American College of Cardiology* with an impact factor of 21.7.

Journal dual-map overlay is an novel visual analytic method that helps researchers deeply understand the interrelationships of academic literature and their positions within the field by displaying citing and cited journals on two different scientific domain maps[16]. Figure 5 illustrates the relationships between source and target journals. Nodes on the left represent citing journals, while nodes on the right represent cited journals. Labels indicate the subject areas, and lines represent citation paths. The figure shows four citation paths related to DVC research. The orange paths indicate citations from journals in ‘molecular biology and immunology’ to journals in ‘molecular biology and genetics’, while the green paths show citations from ‘medicine, clinical medicine’ journals to those in ‘health, nursing, and medicine’. Additionally, paths in different colors, such as yellow, purple, and blue, highlight interdisciplinary citation relationships, such as those between journals in ‘physics, materials, and chemistry’ with those in ‘ecology and earth Sciences’.

Table 4: Top 10 journals of productivity related to DVC

Rank	Journal	Number of publications	% of 1864	IF(JCR2023)	JCR
1	Nephrology Dialysis Transplantation	57	3.06	4.8	Q1/Q1
2	Atherosclerosis	50	2.68	4.9	Q1/Q1
3	International Journal Of Molecular Sciences	34	1.82	4.9	Q1/Q2
4	Plos One	34	1.82	2.9	Q1
5	Arteriosclerosis Thrombosis And Vascular Biology	33	1.77	7.4	Q1/Q1
6	Kidney International	28	1.50	14.8	Q1
7	Cardiovascular Diabetology	27	1.45	8.5	Q1/Q1
8	Bmc Nephrology	26	1.40	2.2	Q2
9	International Urology And Nephrology	25	1.34	1.8	Q3
10	Nutrition Metabolism And Cardiovascular Diseases	23	1.23	3.3	Q2/Q2/Q2

Table 5: Top 10 journals of co-citation related to DVC

Rank	Co-cited Journal	Number of co-citations	Centrality	IF(2023)	JCR
1	*Circulation*	1290	1.03	35.5	Q1/Q1
2	*Arteriosclerosis, Thrombosis, and Vascular Biology*	1063	0.96	7.4	Q1/Q1
3	*Kidney International*	1003	0.49	14.8	Q1
4	*Nephrology Dialysis Transplantation*	953	0.92	4.8	Q1/Q1
5	*Atherosclerosis*	925	0.06	4.9	Q1/Q1
6	*Journal of the American Society of Nephrology*	911	0.12	10.3	Q1
7	*Journal of the American College of Cardiology*	868	0.23	21.7	Q1
8	*Circulation Research*	789	0.18	16.5	Q1/Q1/Q1
9	*New England Journal of Medicine*	788	0.28	96.2	Q1
10	*American Journal of Kidney Diseases*	710	1.06	9.4	Q1

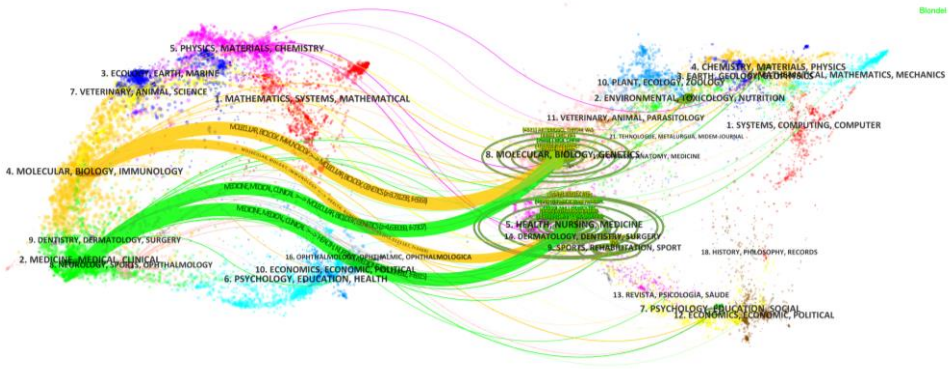

Figure 5: Dual-map overlay of journals related to DVC

3.5. Cited Articles and Co-cited References Analysis

Table 6 lists the top 10 most cited publications, which address topics such as the regulation of vascular smooth muscle cell calcification and the impact of chronic kidney disease on cardiovascular health. The most frequently cited publication is 'Phosphate Regulation of Vascular Smooth Muscle Cell Calcification[17]' by Shuichi Jono, published in *Circulation Research* in 2000, with 1,164 citations. The most cited recent publication is 'Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options[18]' by Jankowski, J., published in *Circulation* in 2021, with 699 citations. This trend indicates a shift from fundamental research on vascular calcification mechanisms to more focused studies on clinical applications, biomarkers, and advanced therapeutic strategies. This shift highlights the field's ongoing development and adaptation to new medical challenges.

A total of 53,533 co-cited references were identified. Table 7 presents the top ten most co-cited references. The most frequently co-cited reference is 'Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness[19]' by Andrew L. Durham, published in *Cardiovascular Research* in 2018, with 42 co-citations. The most co-cited recent article is 'vascular calcification—new insights into its mechanism[2]' by Sun Joo Lee, published in *International Journal of Molecular Sciences* in 2020, with 32 co-citations. These research themes reflect a transition from early studies on vascular calcification in end-stage renal disease patients and its clinical implications to more in-depth exploration of cellular and molecular mechanisms, as

well as the development of biomarkers.

Figure 6A illustrates the research topic clustering of the references, where each cluster consists of multiple closely related terms. The smaller the number, the more keywords it contains within that cluster. There are a total of 18 clusters. The five largest clusters are “cluster #0 peripheral artery calcification”, “cluster #1 omics research”, “cluster #2 diabetes heart study”, “cluster #3 molecular mechanism” and “cluster #4 serum osteoprotegerin level”. In the past five years, research topics have focused on “cluster #1 omics research”, “cluster #3 molecular mechanism”, “cluster #9 Vitamin K” and “cluster #15 translational opportunities”.

Citation burst analysis highlights the focus areas of researchers within a specific field over time[20]. Figure 6B displays the top 25 articles with the strongest citation bursts in the DVC research area. The first citation burst occurred in 2002, with all top 25 references showing a citation burst strength greater than ten. The publication with the highest and longest-lasting citation burst strength is ‘medial vascular calcification revisited: review and perspectives[21]’ by Lanzer, P., published in *European Heart Journal* in 2014, with a burst strength of 20.16 from 2015 to 2019. The highest citation burst strength in the past five years is for ‘role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness[22]’ by Andrew L. Durham, published in *Cardiovascular Research* in 2018, with a burst strength of 18.73 from 2020 to 2024.

Table 6: The top 10 most cited articles related to DVC

Rank	Author	Year	Journal	Title	Citation
1	Shuichi Jono	2000	Circulation Research	Phosphate regulation of vascular smooth muscle cell calcification	1164
2	Ernesto L. Schiffrin	2007	Circulation	Chronic kidney disease - Effects on the cardiovascular system	1160
3	Paolo Raggi	2002	Journal of the American College of Cardiology	Cardiac calcification in adult Hemodialysis patients - A link between end-stage renal disease and cardiovascular disease?	959
4	Guido A. Rosito	2008	Circulation	Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample - The framingham heart study	804
5	Rebecca C. Johnson	2006	Circulation Research	Vascular calcification - Pathobiological mechanisms and clinical implications	740
6	Fellype C. Barreto	2009	Clinical Journal of the American Society of Nephrology	Serum Indoxyl Sulfate Is Associated with Vascular Disease and Mortality in Chronic Kidney Disease Patients	709
7	Moeen Abedin	2004	Arteriosclerosis, Thrombosis, and Vascular Biology	Vascular calcification - Mechanisms and clinical ramifications	702
8	Joachim Jankowski	2021	Circulation	Cardiovascular Disease in Chronic Kidney Disease Pathophysiological Insights and Therapeutic Options	699
9	Geoffrey Block	2007	Kidney International	Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients	585
10	Peter Lanzer	2014	European Heart Journal	Medial vascular calcification revisited: review and perspectives	510

Table 7: The top 10 most co-cited references related to DVC

Rank	Author	Year	Journal	Reference	Co-citation
1	Andrew L. Durham	2018	*Cardiovascular Research*	Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness	42
2	Kazuyuki Yahagi	2017	*Arteriosclerosis, Thrombosis, and Vascular Biology*	Pathology of Human Coronary and Carotid Artery Atherosclerosis and Vascular Calcification in Diabetes Mellitus	40
3	Peter Lanzer	2014	European Heart Journal	Medial vascular calcification revisited: review and perspectives	40
4	Gerard M. London	2003	Nephrology, Dialysis, Transplantation	Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality	37
5	Sun Joo Lee	2020	International Journal of Molecular Sciences	Vascular Calcification-New Insights Into Its Mechanism	32
6	Jane A. Leopold	2015	Trends in Cardiovascular Medicine	Vascular calcification: Mechanisms of vascular smooth muscle cell calcification	28
7	Jing Chen	2017	JAMA Cardiology	Coronary Artery Calcification and Risk of Cardiovascular Disease and Death Among Patients With Chronic Kidney Disease	28
8	Andrew Sage	2010	Nature Reviews Cardiology	Regulatory mechanisms in vascular calcification	28
9	Severine Evrard	2015	Clinical Chimica Acta	Vascular calcification: from pathophysiology to biomarkers	27
10	Glenn M. Chertow	2002	Kidney International	Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients	27

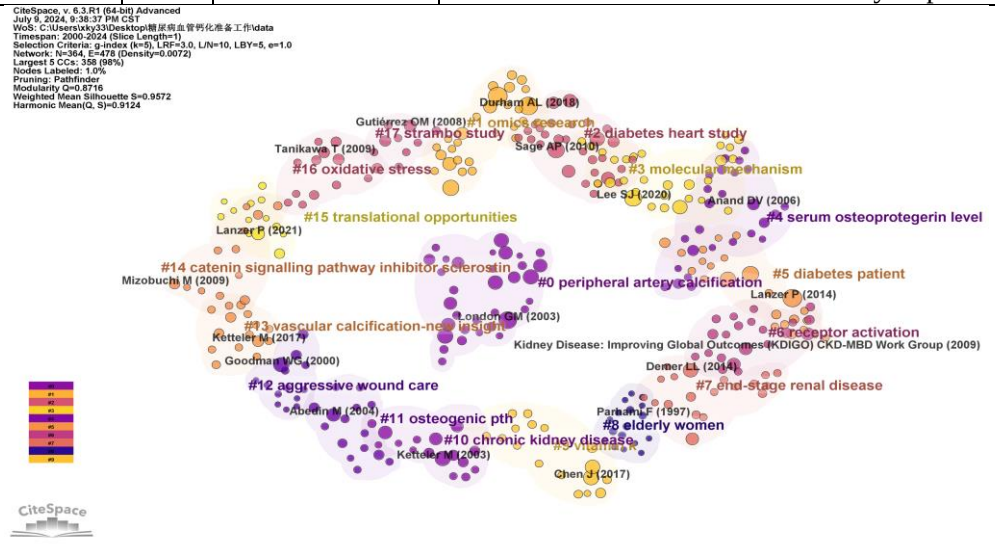

Figure 6A: Clustering map of references related to DVC. The gradient of cluster colors represents the time period during which the research themes were published. The color transition from dark to light reflects the publication time of the references, with darker colors indicating earlier publications and lighter colors indicating more recent ones.

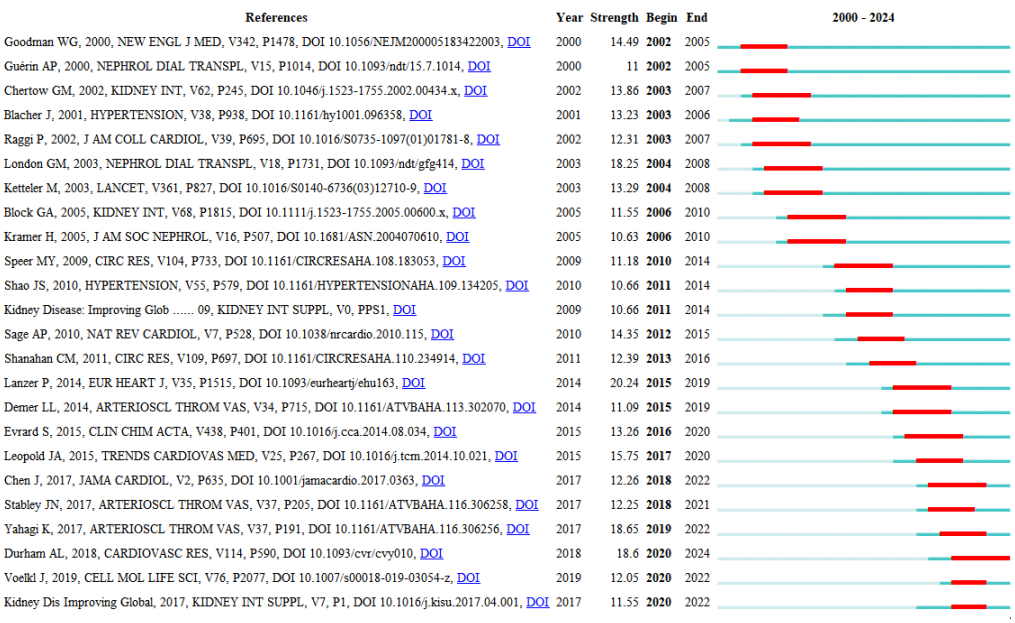

Figure 6B: Top 25 references with the strongest citation bursts

3.6. Keyword Analysis

Keywords are designed to reflect the themes of articles and highlight their key content and focus areas. Using CiteSpace, we performed a statistical analysis of the keywords in the literature and consolidated similar high-ranking keywords. Table 8 presents the top ten most frequent keywords. The keywords with the highest frequency include ‘vascular calcification’, ‘chronic kidney disease’, ‘cardiovascular disease’, ‘association" and "mortality’. These terms represent the current hot topics in DVC research.

Table 8: Top 10 keywords related to DVC

Rank	Year	Keywords	Count	Centrality
1	2000	vascular calcification	1104	0.05
2	2005	chronic kidney disease	434	0.03
3	2000	cardiovascular disease	375	0.04
4	2000	association	275	0.06
5	2004	mortality	271	0.04
6	2004	risk factor	264	0.05
7	2000	atherosclerosis	257	0.03
8	2004	smooth muscle cell	246	0.06
9	2000	diabetes mellitus	198	0.04
10	2003	hemodialysis patient	152	0.03

Keyword burst analysis can review and predict the periodic hotspots and developmental trends in DVC research. Figure 7A shows the top 15 keywords with the highest burst intensity. The keyword with the strongest and longest-lasting burst is ‘beam computed tomography’ with a burst intensity of 17.28 from 2000 to 2009. This indicates the crucial role of imaging diagnostic technology in early DVC research and its importance in advancing scientific research in this field. In the past five years, keywords such as ‘apoptosis’, ‘osteogenic differentiation’, ‘endoplasmic reticulum stress’, ‘hemodialysis’ and ‘death’ have marked emerging areas and important focal points in DVC research.

Figure 7B presents the thematic clusters of keywords, with a total of nine major clusters, including ‘cluster #0 vascular smooth muscle cells’, ‘cluster #1 peripheral artery disease’, ‘cluster #2 FGF23’, ‘cluster #3 bone mineral density’, ‘cluster #4 diabetes mellitus’, ‘cluster #5chronic kidney disease’, ‘cluster #6 Vitamin K’, ‘cluster #7 vascular stiffness’ and ‘cluster #8 vascular calcification’. These keyword clusters reveal that DVC-related research encompasses multiple disciplines such as chronic kidney disease, peripheral artery disease, cardiovascular disease, and bone metabolism diseases, reflecting the multidimensionality and complexity of DVC research.

Figure 7C, by showing the evolution of keywords over time, reveals the fundamental knowledge structure and developmental trajectory of research topics. The research progress of ‘cluster #6 Vitamin K’ and ‘cluster #6 chronic kidney disease’ has stalled in the past five years, possibly indicating that these fields have reached research saturation or have shifted to new research themes. In contrast, other clusters continue to develop and remain active, indicating that these fields are still producing new scientific discoveries and technological innovations.

Figure 7D demonstrates the evolution of hotspots in cardiovascular disease research from 2000 to 2024. Early research hotspots focused on the fundamental pathology of ‘atherosclerosis’ and ‘vascular calcification’. ‘Chronic kidney disease’, as a common complication of diabetes, also received widespread attention during this period. As research deepened, core diabetic pathological mechanisms such as ‘insulin resistance’, ‘inflammation’, and ‘mineral metabolism’ began to receive more attention. Researchers also started to explore the significant impact of changes in ‘vascular smooth muscle cells’ on vascular calcification. From 2011 to 2015, research hotspots gradually shifted to ‘oxidative stress’ and ‘glycation end products’, whose critical roles in diabetic complications were widely discussed. At the same time, the regulatory role of ‘parathyroid hormone’ and ‘vascular smooth muscle cells’ in the calcification process became a research focus. After 2016, research on ‘endoplasmic reticulum stress’ and ‘osteogenic differentiation’ has gradually increased.

Keywords	Year	Strength	Begin	End	2000 - 2024
beam computed tomography	2000	17.28	2000	2009	
dialysis	2001	5.93	2001	2011	
stage renal disease	2002	13.34	2002	2012	
young adult	2004	8.79	2004	2009	
cardiovascular mortality	2000	8.08	2004	2010	
c reactive protein	2004	7.64	2004	2011	
matrix gla protein	2004	6.18	2004	2007	
serum	2004	5.65	2004	2010	
mineral metabolism	2007	5.49	2007	2011	
plasma osteoprotegerin	2009	4.64	2009	2011	
serum osteoprotegerin	2010	4.85	2010	2013	
vitamin d	2006	4.74	2010	2011	
fibroblast growth factor 23	2010	6.06	2012	2018	
high glucose	2012	4.71	2012	2016	
gene expression	2001	5.1	2013	2018	
postmenopausal women	2004	6.01	2014	2018	
kidney disease	2008	5.5	2014	2019	
growth factor 23	2012	5.22	2014	2018	
apoptosis	2006	5.16	2016	2020	
osteogenic differentiation	2014	4.92	2018	2024	
endoplasmic reticulum stress	2019	5.76	2019	2024	
hemodialysis	2008	5.43	2019	2022	
management	2014	5.81	2021	2024	
death	2021	4.9	2021	2024	

Figure 7A: Top 15 keywords with the strongest citation bursts related to DVC

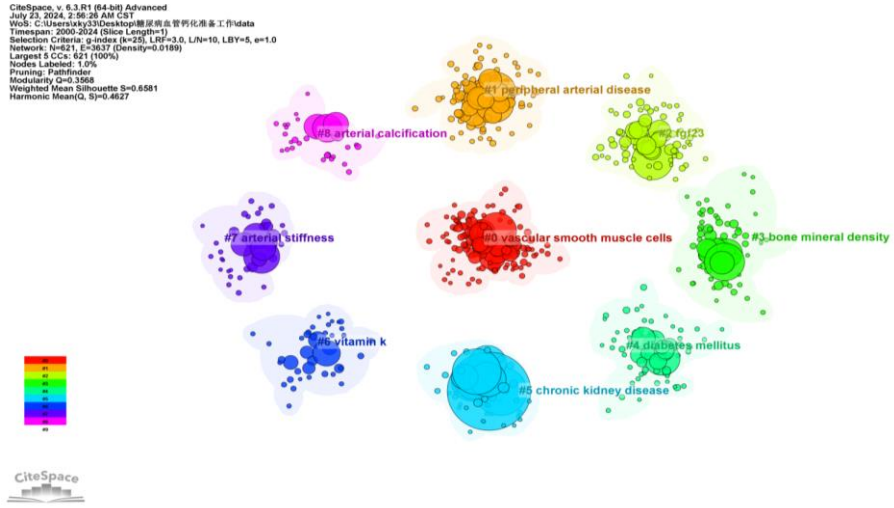

Figure 7B: Clustering map of keywords related to DVC

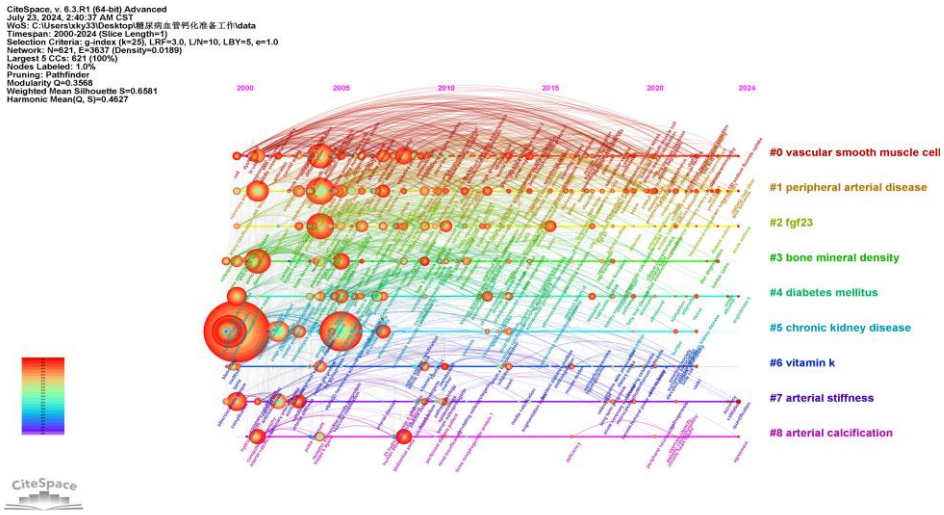

Figure 7C: Keyword timeline graph related to DVC

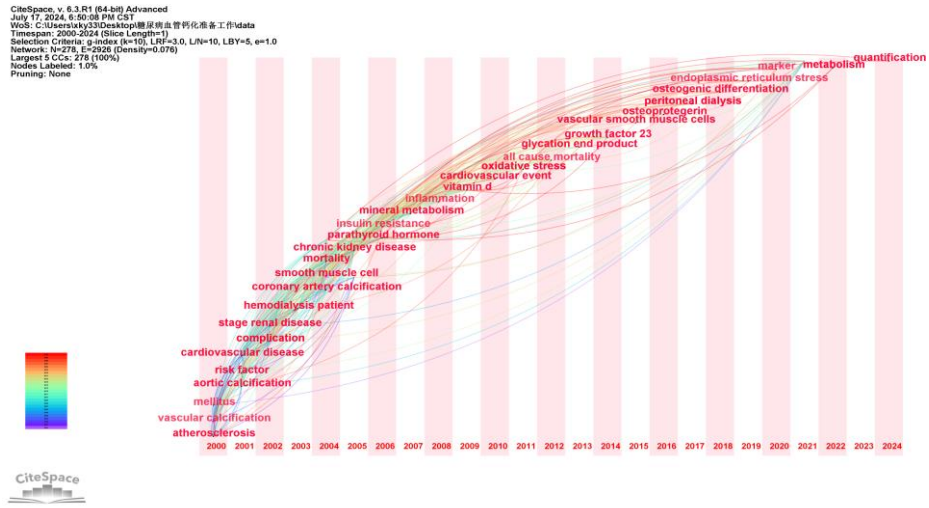

Figure 7D: Keyword time zone map related to DVC

4. Discussion

4.1. General Information

The volume of publications over a certain period intuitively reflects the research activity and development speed in a particular field. The number of publications in the DVC research field has shown a continuous growth trend from 2000 to 2024, especially after 2010, with a significant increase in annual publications. This indicates that DVC research is receiving increasing attention and emphasis from scholars, with growing research intensity.

A total of 71 countries/regions have participated in DVC research. The United States has published the most articles (506 publications), followed by China (361 publications), Japan (162 publications), the United Kingdom (126 publications), and Germany (115 publications). The United States, China, Germany, and the United Kingdom have significant influence in this field, and there is extensive collaboration among these countries/regions. In the future, it is necessary to strengthen international cooperation to promote the development of this research field.

In the author collaboration network, it is noteworthy that Dwight J. Fowler has a citation count far exceeding other authors. His research, entitled ‘Msx2 promotes cardiovascular calcification by activating paracrine Wnt signals’, is of particular interest. This paper deeply explores the relationship between the ectopic BMP2-Msx2 gene regulatory program and vascular calcification in diabetic LDLR-/- mice. The study found that the expression of Msx2 promotes vascular calcification by activating paracrine Wnt signals. More importantly, inhibiting Msx2 or its downstream Wnt signaling pathway can effectively reverse the vascular calcification process[23]. The high citation rate of this article reflects its innovation and impact.

The impact factor of a journal is widely accepted and recognized internationally as an important indicator of the academic influence of a journal. The top-ranked journals in this field include *Nephrology Dialysis Transplantation*, *Atherosclerosis*, *International Journal of Molecular Sciences*, *PLOS One* and *Arteriosclerosis Thrombosis and Vascular Biology*. These journals have significant influence and status in the DVC research field.

Keywords in literature provide a core summary of the research content. Many scholars use keywords from literature in specific fields to analyze research themes and hotspots at different periods, revealing changes in research content and focus in particular fields. Keyword co-occurrence analysis shows that the top-ranked keywords are ‘vascular calcification’, ‘chronic kidney disease’, ‘cardiovascular disease’, ‘association’ and ‘mortality’. Keyword clustering analysis forms nine clusters, including ‘peripheral artery disease’, ‘FGF23’, ‘bone mineral density’, ‘diabetes mellitus’, ‘chronic kidney disease’, ‘Vitamin K’, ‘vascular stiffness’ and ‘vascular calcification’, to identify hotspots and research trends in the DVC research field.

4.2. Hotspots and Frontiers

4.2.1. Basic Research

‘Cluster #0 Vascular Smooth Muscle Cells’ represents the largest cluster. In 2004, the keyword ‘smooth muscle cell’ first appeared, indicating that this field had begun to receive significant attention. The phenotypic transition of VSMCs is a crucial mechanism in vascular calcification. Under normal conditions, VSMCs primarily maintain a contractile phenotype, participating in the regulation of vascular tone and blood flow. However, under certain pathological conditions, VSMCs undergo a significant phenotypic transition to become osteoblast-like cells, a process essential for vascular calcification[19]. In environments with high glucose and other stimuli, VSMCs' phenotypic transition is characterized by the expression of osteogenic markers such as osteopontin

(OPN)[24], osteoprotegerin (OPG)[25], runt-related transcription factor 2 (RUNX2)[26], and bone morphogenetic protein-2 (BMP-2)[27]. The expression of these osteogenic markers promotes the deposition of calcium salts within the vascular wall, thereby accelerating the process of vascular calcification. In 2012, the keyword "high glucose" first appeared, indicating a surge in research on VSMC phenotypic transition induced by high glucose environments. These studies involve various cell signaling pathways, such as Wnt/β-catenin, HIF-1α/PDK4, RAGE/p38 MAPK, and RANKL/RANK, which play critical roles in the transition of VSMCs to an osteoblast-like phenotype. In 2019, the keyword ‘endoplasmic reticulum stress (ERS)’ first appeared, highlighting researchers' growing interest in the critical role of ERS in VSMC osteogenic differentiation and calcification. ERS refers to a series of cellular stress responses caused by the accumulation of misfolded or unfolded proteins within the endoplasmic reticulum. In a high glucose environment, ERS activates the unfolded protein response (UPR) to maintain cellular homeostasis. However, prolonged ERS can lead to cellular dysfunction, promoting the osteogenic differentiation and calcification of VSMCs. ERS regulates gene expression through various signaling pathways, such as the PERK/eIF2α/ATF4, SIRT1, and ATF4 pathways, enhancing the production of osteogenic markers and ultimately leading to vascular calcification. Currently, researchers have developed several ERS inhibitors considered potential therapeutic agents.

4.2.2. Clinical Research

‘Cluster #1 peripheral arterial disease’ ranks second in keyword clustering indicates that it is a hot topic in the field of DVC research. PAD is a common atherosclerotic disease that primarily affects the arteries of the lower extremities. Studies have shown that the coexistence of PAD and DVC significantly increases the cardiovascular risk in patients. Medial arterial calcification (MAC) is an independent risk factor for PAD, particularly linked to higher amputation rates, mortality, and it foretells adverse outcomes following endovascular interventions. In 2015, O'Neill and colleagues performed a histological evaluation of 176 arterial samples from 60 patients diagnosed with peripheral arterial disease, the majority of whom had diabetes, end-stage renal disease, or additional risk factors associated with PAD.The results showed that 72% of the samples experienced medial calcification, 68% had intimal thickening without lipid deposition, and intimal calcification was found in 43% of the arterial samples, which was generally much less extensive than medial calcification. Atherosclerotic plaques were observed in only 23% of the samples. The ankle-brachial index (ABI) is a commonly used tool for assessing PAD, typically employed to detect narrowing or blockage in the lower limb arteries. Studies have shown that a low ABI (<0.90) is generally associated with the presence of PAD, while a high ABI (>1.40) may indicate arterial stiffness and MAC, but there is a high rate of false positives in the diagnosis of high ABI. In recent years, researchers have shown great interest in the effectiveness of intravascular lithotripsy (IVL) for treating PAD. A randomized controlled trial in 2021 evaluated the short-term outcomes of IVL in patients with calcified femoropopliteal arteries. The results indicated that IVL is an effective and safe vessel preparation strategy for treating calcified femoropopliteal arteries in PAD, demonstrating higher procedural success rates and fewer complications compared to percutaneous transluminal angioplasty (PTA).

4.2.3. DVC and Chronic Kidney Disease

CKD is a common chronic illness, particularly prevalent among diabetic patients, where the incidence of CKD is significantly elevated. In 2000, a study by John S. et al. first revealed that elevated phosphate levels can directly stimulate phenotypic changes in human aortic smooth muscle cells, promoting the development and progression of vascular calcification. Elevated serum

phosphate levels are a late manifestation of CKD and have been shown to accelerate mineral deposition in the vascular walls and heart valves. The excessive cardiovascular mortality associated with CKD is partly attributed to CKD-mineral and bone disorder (CKD-MBD). Currently, the clinical management of CKD-MBD primarily involves the use of phosphate binders, vitamin D, and parathyroid hormone (PTH) modulators (e.g., cinacalcet). In recent years, Wnt signaling pathway inhibitors, such as Dickkopf-1 (Dkk1) and sclerostin, have been implicated in the pathogenesis of CKD-MBD, providing potential targets for the development of new therapeutic strategies.

4.2.4. DVC and Bone disease

Osteoporosis and vascular calcification often co-occur in the elderly, particularly in postmenopausal women. This phenomenon is referred to as the ‘calcium paradox’, which describes the coexistence of vascular calcification with reduced bone mass or disordered bone remodeling in osteoporosis. In 2022, Wang et al. revealed the critical role of aging bone matrix extracellular vesicles (AB-EVs) in this pathological process. They found that AB-EVs can migrate to bone marrow and vascular tissues, inducing adipogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) and promoting osteogenic transdifferentiation of VSMCs. These processes not only lead to bone-fat imbalance but also exacerbate vascular calcification. Therefore, the role of AB-EVs in osteoporosis and vascular calcification provides new therapeutic targets and research avenues for the treatment of age-related skeletal and vascular diseases.

4.2.5. DVC and fibroblast growth factor 23

According to keyword prominence analysis, ‘FGF23’ had high attention from 2012 to 2018, indicating its importance and hot status in biomarker research in the DVC field. FGF23 is a growth factor produced by osteocytes, primarily functioning to regulate phosphate and calcium homeostasis by stimulating urinary phosphate excretion and inhibiting circulating calcitriol levels. Some studies have shown that elevated FGF23 levels are closely associated with the occurrence and progression of vascular calcification. In patients with CKD, significantly elevated FGF23 levels are considered a compensatory mechanism to manage hyperphosphatemia. However, high levels of FGF23 have also been observed to correlate with the severity of vascular calcification. Nevertheless, not all studies support the view that FGF23 promotes vascular calcification. Some studies have failed to find a significant association between FGF23 and vascular calcification, and a few even suggest that elevated FGF23 levels might have a protective effect. Therefore, larger-scale studies are still needed to clarify the mechanisms of FGF23 in vascular calcification and to explore its potential value in clinical applications.

4.2.6. DVC and Vitamin K

Since 2004, research on vitamin K in the VC field has been ongoing. Supplementing with vitamin K2 (MK-7) can increase the levels of carboxylated matrix Gla protein (MGP), which acts as a central inhibitor of arterial calcification. Although some randomized trials have suggested that vitamin K supplementation can significantly reduce the levels of desphospho-uncarboxylated MGP (dp-ucMGP), the evidence for the role of vitamin K in DVC appears to be inconsistent, particularly in patients with DVC, where vitamin K has not demonstrated effective action. This suggests that the role of vitamin K in the treatment of DVC may require further research for clarification.

5. Strengths and Limitations

This study represents the first bibliometric analysis of publications related to DVC over the past

20 years. Unlike traditional systematic reviews, bibliometric analysis objectively presents research hotspots and trends in this field through visualization techniques. However, the study has some limitations. Due to constraints in the database and time range, it may not cover all relevant research. Specifically, only the Web of Science Core Collection database was searched up to June 30, 2024, potentially omitting some of the latest literature. Additionally, the diversity of research topic terminology and issues with the completeness of the literature might affect the accuracy of the analysis. The software used for keyword extraction might not be exhaustive, and some relevant literature may have been excluded during the screening process, potentially affecting the completeness of the results. Finally, the inherent limitations of bibliometric methods should also be considered when interpreting the results.

6. Conclusion and Outlook

Research on DVC is transitioning from basic biology to clinical applications, emphasizing the urgency of translating scientific discoveries into therapeutic strategies. Emerging biomarkers such as FGF23 provide new indicators for early diagnosis and treatment. The multidisciplinary nature of DVC requires comprehensive prevention and treatment strategies, particularly considering its comorbidity with other chronic diseases. The United States and China have played significant roles in promoting international cooperation. Journal and co-citation analyses have highlighted authoritative journals and foundational research, providing guidance for future research directions. DVC research is moving towards a comprehensive, personalized, and precision medicine approach. Global participation should be encouraged to enrich scientific perspectives and drive scientific and clinical innovation.

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