# Original Article Global trends in the research of hypertrophic cardiomyopathy: a bibliometric and visualized study

Jiahua Liang<sup>1\*</sup>, Xilian Feng<sup>1\*</sup>, Yinuo Fan<sup>1</sup>, Chuangxiong Hong<sup>2</sup>

<sup>1</sup>The First Clinical Medical College, Guangzhou University of Chinese Medicine, 12 Jichang Road, Baiyun District, Guangzhou 510405, Guangdong Province, China; <sup>2</sup>The Department of Cardiovascular Disease, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510405, Guangdong Province, China. <sup>\*</sup>Equal contributors and co-first authors.

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Abstract: Background: Hypertrophic cardiomyopathy (HCM) is a genetic disorder with widespread global reach. Methods: The Web of Science database was used to search the relevant English literature for HCM from 2010 to July 1, 2020. The search utilized bibliometrics methods, quality assessment of the publications from different countries, authors, institutions, funding agencies, and journals. VOS viewer software was utilized for visual conversions, research directions and hotspot fields for HCM, simultaneously. Results: The quantity of published articles regardingHCM is growing steadily. As for funding agencies, there are more funding agencies to support research on HCM in the United States. In terms of journals, the AMERICAN JOURNAL OF CARDIOLOGY publishes the most, and the published articles from the JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY are of the highest quality. As for different contributing countries, the USA is ahead in quantity and quality of published articles. With regard to institutions, MAYO CLINC publishes the largest amount of research, but the published articles of HARVARD UNIVERSITY are of the highest quality. Via co-occurrence analysis, the global research direction in the field of HCM consists of four categories, Epidemiology, Pathogenesis, Diagnosis and Treatment. Conclusions: The United States leads the research for HCM, and China also has active publication performance in this field. Scholars are advised to pay more attention to the research progress of the United States in this field, and cooperate with the top authors or institutions to deepen HCM related research. Understanding current research hotspots is necessary for future development of HCM therapy and treatment.

Keywords: Bibliometrics, visual analysis, hypertrophic cardiomyopathy, co-occurrence analysis

#### Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart diseases with an incidence of about 1/500 [1]. HCM is defined as a wall thickness  $\geq$ 15 mm of one or more left ventricular myocardial segments [2]. Clinical diagnosis requires echocardiography or cardiovascular cardiac magnetic resonance to show the hypertrophic tissue, most of which is the left ventricle [3, 4]. The phenotypic expression of HCM may vary greatly in terms of age, severity, presence of left ventricular outflow tract (LVOT) obstruction, and prognosis. The life expectancy of most HCM patients is close to the average person. Some patients with HCM will have symptoms that require treatment and thus choosing the most appropriate treatment depends on the pathophysiology of each patient. This may be multifactorial, including HCM related mechanisms such as systolic or diastolic dysfunction, LVOT obstruction, myocardial ischemia due to mitral regurgitation or arrhythmia, as well as some other non-HCM-related mechanisms [5].

However, there is no bibliometric analysis to report the current status of HCM research and global development trends. Bibliometrics is a statistical method used to quantitatively evaluate developmental trends in the research, based on literature databases and their characteristics including journals, institutions, countries and so on, providing evidence for the development of clinical guidelines and future research directions of specific research fields [6]. The purpose of this study is to analyze the status of global HCM related publications in order to carry out layered refinement and quality assessment of the publications in different countries, authors, institutions, funding agencies, and journals. In addition, we also performed a co-occurrence analysis of keywords from HCM related publications in order to understand their research directions and hotspot areas.

# Method

Web of Science's Science Citation Index Expanded (SCI-E) database was used for bibliometric analysis [7, 8]. Through an advanced search, the timeframe was from 2010 to June 27, 2020. Then we entered "hypertrophic cardiomyopathy" and its free words retrieved the required English literature, and we obtained the information regarding the retrieved documents, including authors, countries, journals, institutions, annual publications, and funding agencies. We then downloaded and saved the information to TXT format and imported it into the 2019 version of Microsoft Excel for analysis to ensure that the information is correct. Subsequently, two independent researchers (Jiahua Liang, Xilian Feng) separately verified and evaluated the data, and unified the opinions through discussion. Finally, the subsequent literature measurement parameters were determined: Total Publications, Sum of Times Cited, Average citations per item, H-index (Journals including IF).

# Bibliometric analysis

Web of Science allows analysis of the retrieved literature. The retrieved results were analyzed and extracted separately for funding agencies, journals, literature related to authors, countries, and institutions. The data for the measurement parameters are tabulated. The frequency of citations represents the total number of citations in the corresponding years. H-index is the number of publications which have been cited at least H times. This reflects the quantity and quality of the published articles by researchers and institutions [9, 10]. Average citations per item are the average number of citations per article, and this can also represent the quality of the publication to some extent. The IF of a journal represents its influence.

# Visual analysis

VOS viewer software (version 1.6.11) created by Netherlands Leiden University was utilized for visual analysis of the literature. The .txt file containing all the literature information that was obtained from the Web of Science database was imported into the software for "cooccurrence analysis", and the network and overlay visualization analysis structure diagrams were separately exported. Co-occurrence analysis can be employed to discern current research directions and hotspot areas of research.

# Results

A total of 11045 documents were searched on the Web of Science, and 6112 documents were finally included, as shown in **Figure 1** of the explicit inclusion and exclusion criteria chart.

# Number of global publications

From 2010 to 2020, the quantity of HCM articles has been growing steadily. It can be seen from **Figure 2** that the volume of annual articles can be divided into two periods: the first period is from 2010 to 2016, and the second period is from 2017 to 2020. In the first period, the rate of publications fluctuated slightly with the annual growth in publications rising and falling, but with an overall upward trend. In the subsequent period, the publication of the literature seems to have dropped slightly.

# Assessment of global publications

Funding agencies: A total of 4361 funding sources supported research in this area, which is ranked in the top 10 as shown in **Table 1**, and these funding agencies supported nearly 56% of the research. Interestingly, nearly half of the funding agencies come from the United States, the rest are from the China, Britain, the European Union, Japan and France. The topranked was the United States Department Of Health Human Services 1019 studies (16.672%), followed by National Institutes of Health NIH, USA (1015 studies, 16.607%) and National Natural Science Foundation Of China (326 studies, 5.334%).



Figure 1. The inclusion and exclusion process of Hypertrophic cardiomyopathy research.



Figure 2. Number of publications per year.

#### Journals

A total of 969 journals published research on HCM. **Table 2** displays the top 10 journals in terms of the number of publications, which published about 16.12% of the literature. Analyzed in terms of the number of publications, the AMERICAN JOURNAL OF CARDIOLOGY is the most prominent journal, with the most published journal with 195 articles, followed by PLOS ONE (131 articles) and INTERNATIONAL JOURNAL OF CARDIOLOGY (117 articles). In terms of quality: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY (H-index 50, Sum of Times Cited 7089, Average citations per item 79.65. IF 23.603) was the highest quality, followed by CIRCULATION (H-index 44, Sum of Times Cited 7921, Average citations per item 80.83. IF 20.589) and the AMERICAN JOURNAL OF CAR-DIOLOGY (H-index 29, Sum of Times Cited 2753, Average citations per item 14.12. IF 2.570). Not surprisingly, the overall quality of these 10 journals is high, with IFs mostly above 2.

#### Authors

About 28461 authors have contributed to HCM-related research. Table 3 lists the top 10 authors who are most active in the field of HCM. In terms of the number of articles published, the top three are MARON BJ (111 articles), MARON MS (89 articles), and OMMEN SR (88 articles); from the analysis of the quality of the articles, we presume that MARON BJ (H-index 41, Sum of Times Cited 5997, Average citations per item 54.03) had the highest quality of articles, followed by MARON MS (H-index 32, Sum of Times Cited 3697, Average citations per item 41.54) and OMMEN SR (H-index 29, Sum of Times Cited 3816 Average citations per item 43.36). There is no doubt that the num-

ber of citations by each author is not necessarily proportional to the quality of the citations.

#### Countries

Currently, 70 countries have published relevant studies on HCM. The top 10 countries/areas in terms of the number of publications is listed in **Table 4**. In terms of the number of articles issued, the USA (2427) issued the most articles, followed by England (732) and China (642). Analyzed in terms of text quality, USA still leads in text quality (H-index 48, Sum of Times Cited 54094, Average citations per item 22.29), England (H-index 70, Sum of Times Cited 22003, Average citations per item 30.06)

Ranking	Fund source	Total Publications	Ranking	Fund source	Total Publications
1	UNITED STATES DEPARTMENT OF HEALTH HUMAN SERVICES	1019	6	BRITISH HEART FOUNDATION	206
2	NATIONAL INSTITUTES OF HEALTH NIH USA	1051	7	EUROPEAN UNION EU	134
3	NATIONAL NATURAL SCIENCE FOUNDATION OF CHINA	326	8	MINISTRY OF EDUCATION CULTURE SPORTS SCIENCE AND TECHNOLOGY JAPAN MEXT	119
4	AMERICAN HEART ASSOCIATION	286	9	MEDICAL RESEARCH COUNCIL UK MRC	115
5	NIH NATIONAL HEART LUNG BLOOD INSTI- TUTE NHLBI	242	10	LEDUCQ FOUNDATION	106

#### Table 1. The top 10 fund sources

#### Table 2. The top 10 journals with most publications from 2010 to 2020

Ranking	Journal	Total Publications	Sum of Times Cited	Average citations per item	H index	IF
1	AMERICAN JOURNAL OF CARDIOLOGY	195	2753	14.12	29	2.570
2	PLOS ONE	131	1785	13.63	24	2.740
3	INTERNATIONAL JOURNAL OF CARDIOLOGY	117	1353	11.56	19	3.229
4	JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY	105	1823	17.36	26	4.133
5	ECHOCARDIOGRAPHY A JOURNAL OF CARDIOVASCULAR ULTRASOUND AND ALLIED TECHNIQUES	100	811	8.11	13	1.393
6	CIRCULATION	98	7921	80.83	44	23.603
7	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	89	7089	79.65	50	20.589
8	HEART	80	2816	35.2	28	5.213
9	INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING	76	721	9.49	16	1.969
10	AMERICAN JOURNAL OF PHYSIOLOGY HEART AND CIRCULA- TORY PHYSIOLOGY	65	826	12.71	18	3.864

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Ranking	Author	Total Publications	Sum of Times Cited	Average citations per item	H index
1	MARON BJ	111	5997	54.03	41
2	MARON MS	89	3697	41.54	32
3	OMMEN SR	88	3816	43.36	29
4	OLIVOTTO I	80	2550	31.88	26
5	ACKERMAN MJ	69	3621	52.48	27
6	MICHELS M	64	1466	22.91	20
7	NISHIMURA RA	60	3224	53.73	24
8	SEMSARIAN C	58	2472	42.62	24
9	ELLIOTT PM	57	5926	103.96	23
10	SEIDMAN CE	55	4608	83.78	28

Table 3. The top 10 active authors with most publications from 2010 to 2020

and Germany (H-index 62, Sum of Times Cited 15400, Average citations per item 28.21) followed. Although China has published numerous articles, there is room for improvement in quality of the articles.

#### Institutions

About 5853 institutions have published articles in this field and **Table 5** lists the top 10 institutions in terms of the number of publica-

tions. In terms of the number of publications, it is clear that MAYO CLINC published 219 studies has the most, followed by HARVARD UNIVERSITY (152 articles) and UCLA (149 articles); an analysis of the quality of the articles leaves no doubt as to HARVARD UNIVERSITY (H-index 47, Sum of Times Cited 8276, Average citations per item 54.45) published articles of the highest quality, followed by BRIGHAM WOMENS HOSPITAL (H-index 40, Sum of Times Cited 6357, Average citations per item 46.74)

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Ranking	Author	Total Publications	Sum of Times Cited	Average citations per item	H index
1	USA	2427	54094	22.29	93
2	ENGLAND	732	22003	30.06	70
3	PEOPLES R CHINA	642	5153	8.03	30
4	ITALY	564	17064	30.26	61
5	GERMANY	546	15400	28.21	62
6	JAPAN	520	5603	10.78	33
7	NETHERLANDS	325	9682	29.79	53
8	CANADA	315	8739	27.74	48
9	AUSTRALIA	266	7043	26.48	45
10	FRANCE	263	7457	28.35	46

 Table 4. The top 10 countries with most publications from 2010 to 2020

Table 5. The top 10 institutions with most publications from 2010 to 2020

Ranking	Institution	Total Publications	Sum of Times Cited	Average citations per item	H index
1	MAYO CLIN	219	6485	29.61	38
2	HARVARD UNIV	152	8276	54.45	47
3	UCL	149	6692	44.91	37
4	BRIGHAM WOMENS HOSP	136	6357	46.74	40
5	UNIV SYDNEY	126	3554	28.21	29
6	CHINESE ACAD MED SCI	124	1149	9.27	18
7	STANFORD UNIV	114	4739	41.57	33
8	PEKING UNION MED COLL	106	948	8.94	16
9	JOHNS HOPKINS UNIV	99	2615	26.41	22
10	TUFTS MED CTR	99	3629	36.66	32

and MAYO CLINC (H-index 38, Sum of Times Cited 6485, Average citations per item 29.61). HARVARD UNIVERSITY is at the forefront of research in the field of HCM.

#### **Co-occurrence analysis**

# Research direction analysis

All the published literature included in the study has a total of 14849 keywords. Each keyword is defined by its appearance at least 5 times through the VOS viewer software, and a total of 1957 keywords are retained. As shown in **Figure 3**, the research direction of the field is divided into 4 categories: Epidemiology (cluster1, in green), Pathogenesis (cluster2, in red and yellow), Diagnosis (cluster3, in blue) and Treatment (cluster4, in light blue).

The high-frequency keywords in cluster1 are sudden cardiac death, prevention and taskforce. In cluster2, the most frequently occurring keywords are gene, expression and phosphorylation. In cluster3, the most frequently used keywords are echocardiography, diastolic function, and strain. In cluster4, the most commonly used keywords are follow-up, myocardial ablation and practice guidelines.

# Hotspot analysis

The VOS viewer software can be used to classify keywords in the literature according to the chronological order of their appearance, so that their research hot spots are expressed by different colors. As shown in **Figure 4**, it can be seen from the time scale under the figure that the color of purple appears earlier and belongs to the previous research hotspot, followed by light blue, green and yellow, and the latest is red, which is the current research hotspot. The color changes gradually from purple to red. By analyzing the emergence of keywords, we judge that the current research hotspots are involved in four aspects.

# Discussion

At present, there is a mature program for the diagnosis and treatment of HCM. It is neces-

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Figure 3. Co-occurrence analysis of research directions.



Figure 4. Co-occurrence analysis of research hotspot.

sary to review the development of HCM. Bibliometrics can not only provide comprehensive, objective, and macro information, but also find the research directions and hot spots in a certain field [11, 12]. This study is designed to summarize the development of HCM through bibliometrics, evaluate HCM related publications, and visually analyze the research directions and hot spots.

# Assessment of global publications

Between 2010 and 2020, global publications on HCM have grown steadily. Overall, the United States is still a giant in the field of HCM research with more funding agencies and highquality journals. In addition, it is also in a leading position in terms of the quantity and quality of national documents. In terms of the author's contribution to HCM research. MARON BJ made the most contribution with the largest number and the highest quality of published articles. These results give us inspiration. If we want to grasp the latest developments in this field, we can start with the journals with the highest quality of publications. If we consider cooperation issues, the USA and HARVARD UNIVERSITY are preferred. If we want to fund the research of an author to overcome HCM related problems, there is no doubt that MARON BJ's research is worthy of financial support.

# Co-occurrence analysis

# The analysis of research directions and hotspot

The VOS viewer software was used to visualize statistical keyword clusters and global research directions in the field of HCM. By analyzing the emergence of keywords, we judge that the current research hotspots are involved in four major aspects including Epidemiology, Pathogenesis, Diagnosis, and Treatment. We analyze these directions and research hotspots separately.

# Epidemiology

HCM is a global disease [13] that is considered one of the most common genetic heart diseases. The estimated prevalence of HCM is 1/ 500 based on data collected in the landmark CARDIA (Coronary Artery Risk Development in Young Adults) cohort study from about 25 years ago [1]. However, the development of HCM research includes an increase in clinical experience, a deeper understanding of the underlying molecular and genetic substrate, the implementation of contemporary family screening, and the development of diagnostic cardiac imaging, which may possibly underestimate the prevalence of this disease [14]. Some researchers have suggested that, based on the currently available data as well as the contemporary clinical and genetic principles, the combined prevalence of clinically expressed HCM and gene carriers could be revised to about 1/200 [15]. In the future, it is likely that conduction of a comprehensive study, including genetic testing, echocardiography, and CMR (cardiac magnetic resonance) imaging for the purpose of determining the prevalence of HCM will be improved.

# Pathogenesis

Hypercontractility seems to be the center of the pathogenesis of HCM. Most known mutations affect sarcomeric proteins, and about 70% of the identifiable mutations involve cardiac βmyosin heavy chain (MYH7) and myosin-binding protein C (MYBPC) [16, 17]. Myosin contains the ATPase involved in the actin-myosin bridge and muscle fiber shortening, and is associated with the molecular motor of myocardial contraction. It is known that the mutations of MYH7 will affect the activity of myosin ATPases and increase the production of myocardial force, and MYBPC plays a role in the sarcomere tissue and may play a braking role in the contraction of myofibrils [18, 19]. In addition, recent studies have found that pathogenic variants in the mitochondrial genome have been described in the maternally inherited HCM family, proving that non-sarcomere reasons are involved in the pathogenesis of HCM [20].

# Diagnosis

In adults, HCM is defined by a wall thickness ≥15 mm of one or more left ventricular myocardial segments measured by imaging techniques such as echocardiography, cardiac magnetic resonance (CMR) imaging or computed tomography (CT) [2]. The left ventricular ejection fraction (LVEF) of HCM usually increases due to radial thickening, however, in the case of left ventricular hypertrophy, LVEF is not a reliable parameter for systolic function [21]. In recent years, new echocardiographic techniques, such as speckle tracking echocardiography, have provided useful information for evaluating left ventricular systolic function [22, 23]. Recent research suggests that myocardial crypts detected by CMR may be a subtle feature of HCM in patients with positive sarcomere gene mutations [24]. In addition, scholars are gradually paying more attention to nonconventional risk markers of sudden cardiac death (SCD). Global longitudinal strain [25] and the degree of myocardial fibrosis assessed by CMR are also considered as risk factors for SCD [26]. Fragmented QRS complex (fQRS) can be used as a useful marker for predicting ventricular arrhythmia events in HCM, and it seems related to the increase in cardiovascular mortality in HCM [27].

#### Treatment

In recent years, novel pharmacotherapies, minimally-invasive surgery, and gene-directed methods have emerged, which may change the current treatment prospects. Mavacamten is a first-in-class small oral molecule that can lead to reversible inhibitions of actin-myosin cross bridging [28, 29]. Some recent animal experiments and clinical trials have achieved significant results [30-33]. CK-274 (Cytokinetics, Inc., South San Francisco, CA, USA) is a myocardial myosin inhibitor being developed, which will be applied for a phase II clinical trial in obstructive HCM (oHCM). Myosin inhibitors are expected to be utilized. In addition, recent studies have found that sacubitril/valsartan [34] and the sodium-glucose co-transporter 2 inhibitors [35, 36] are effective drugs for the treatment of non-HCM-related systolic heart failure, however, their efficacy in HCM treatment has not been confirmed. Novel procedural techniques are constantly evolving revealing that septal reduction therapy (SRT) has a better effect on patients with oHCM and drug-refractory symptoms. Whereas current SRTs usually cannot resolve the highly prevalent mitral valve lesions in HCM [37-39], some of which have been proven to be independent factors leading to LVOT obstruction [40]. Several new novel procedural techniques try to solve these problems [41]. More recently, it has been reported that 15 patients with symptomatic oHCM treated by percutaneous intramyocardial septal Radiofrequency (RF) ablation had resolved obstruction, improved NYHA class, and reduced serum levels of NT-proBNP at 6 months [42, 43]. There were no cases of complete heart block or bundle branch block. Catheter-based high-intensity focused ultrasound (HIFU) is also attractive because it can effectively produce deeper myocardial damage than RF [44]. Although no one study has solved HCM, HIFU provides the possibility of a complete non-invasive septal reduction in the future. The above new methods may soon provide alternatives for patients with oHCM.

# Limitations

This research has some limitations which may affect the accuracy of statistical results. Firstly, this research is restricted to English literature. Publications related to HCM in other languages were not included in the literature. Secondly, studies are limited to the period up to Jul 1, 2020. Finally, recently published literature may result in a lower number of citations and affect the overall citation frequency and the H-index.

# Conclusion

With the United States currently leading the way in HCM-related research and China having a fairly active presence in the field, it is revealed that scholars can pay more attention to the progress of U.S. research in this area, and collaborate with leading authors or research institutions for major insights in HCM. The current research hotspots are involved in four aspects: Epidemiology, Pathogenesis, Diagnosis and Treatment. Understanding current research hotspots is necessary for future development of better HCM research in the future.

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# Disclosure of conflict of interest

# None.

Address correspondence to: Dr. Chuangxiong Hong, Department of Cardiovascular Disease, Guangzhou University of Traditional Chinese Medicine First Affiliated Hospital, Jichang Road 16#, District Baiyun, Guangzhou 510405, Guangdong, China. E-mail: gzhcx1966@126.com

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