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Frontier and hotspot evolution in Brugada syndrome

A bibliometric analysis from 2002 to 2022

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Abstract

Background: Brugada syndrome (BrS) is a genetic disorder characterized by a typical electrocardiogram pattern and predisposition to arrhythmias and sudden cardiac death. Despite our considerably evolved understanding of BrS, no bibliometrics have been performed in this research field. We aimed to analyze and visualize the characteristics of the scientific outputs, topical evolutions, and research trends of BrS over the past 2 decades using bibliometric analysis.

Methods: The literature associated with BrS was retrieved from the Science Citation Index Expanded of the Web of Science Core Collection database. Acquired data were then visually analyzed using CiteSpace and VOSviewer.

Results: 3042 qualifying records were included in the final analysis. The publication outputs increased over time. The United States was the leading country in the BrS research. The University of Amsterdam (Netherlands) was the most prolific and influential institution. Pedro Brugada, Arthur Wilde, and Charles Antzelevitch exerted notable publication impact and made the most significant contributions in the field of BrS. *Heart Rhythm* had the highest outputs and *Circulation* was the most influential journal. Bundle branch block, ST-segment elevation, mechanism, management, right precordial lead, and guideline were the keywords with the strongest citation burst.

Conclusion: Research on BrS is prosperous. Keywords and co-citation analysis revealed that the mechanism, diagnosis, risk stratification, and management of BrS were the research hotspots. Besides, the underlying pathophysiology, novel therapies, and personalized risk assessment might be the emerging trends of future research.

Abbreviations: BC = betweenness centrality, BrS = Brugada syndrome, ECG = electrocardiogram, ICD = implantable cardioverter defibrillator, Nc = citations without self-citations, Np = number of publications, SCD = sudden cardiac death, VA = ventricular arrhythmia, VF = ventricular fibrillation.

Keywords: arrhythmia, bibliometric analysis, Brugada syndrome, CiteSpace, sudden cardiac death, VOSviewer

1. Introduction

In 1992, the Brugada brothers reported that 8 individuals suffered from sudden cardiac death (SCD) caused by documented ventricular fibrillation (VF). These patients had characteristic electrocardiogram (ECG) changes of ST-segment elevation in the right precordial leads in a structurally normal heart.[1] This disease was initially known as "*right bundle branch block, persistent ST-segment elevation, and sudden death syndrome*" until 1996, when the new clinical entity was named Brugada syndrome (BrS) for the first time.[2,3] In 1997, BrS and sudden unexplained nocturnal death syndrome were recognized as the same disorder.[4] BrS and other primary electrical diseases have common denominator alterations of ionic currents resulting in depolarization and repolarization abnormalities.[5]

BrS typically manifests in the third or fourth decade of life.[6] Most individuals with a Brugada ECG are asymptomatic. A small minority develop ventricular arrhythmias (VAs) that result in trouble breathing, syncope, and even SCD.[6] The familial nature of BrS soon became evident, supporting an autosomal dominant pattern of inheritance.[7] To date, more than 300 mutations associated with BrS have been reported in 19 different genes, which encode sodium, potassium, and calcium channels or associated proteins.[5] In 1998, the first genetic alteration was identified in the *SCN5A* gene, which encodes for the α-subunit of the $Na_V1.5$ sodium channel.[8] It is difficult to

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This bibliometric analysis based on published data. Therefore, ethics approval is not necessary.

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discern the true burden of BrS owing to the unknown prevalence of asymptomatic patients. Nonetheless, the prevalence of BrS is estimated to affect 1 in 2000 worldwide.[9] This condition is more common in males than females and those of Asian descent.[9]

The diagnosis of BrS is a clinical-electrocardiographic one.[5] Three forms of the BrS ECG pattern have historically been described, although only type 1 is considered diagnostic, which consists of coved ST-segment elevation ≥ 2 mm with T-wave inversion in the right precordial leads.[10] No cure for BrS exists, so far. Lifestyle changes are advised including prompt treatment for fever and avoidance of contraindicated substances.[11] An implantable cardioverter defibrillator (ICD) should always be implanted in symptomatic patients, with quinidine and ablation used for patients with recurrent arrhythmia.[9] Notwithstanding progressive understanding of this clinical entity over the last 30 years, comprehensive reports that can benefit scholars to obtain an intuitive overview and reveal research trends are still absent.

Bibliometric analysis is a statistical approach to exploring and analyzing large volumes of scientific data.[12] Combining visualizing processing tools like CiteSpace[13] and VOSviewer,[14] it utilizes published data to identify novel findings and current research trends of a particular topic. Therefore, clinical practitioners and researchers can update the new practices that evoke novel research ideas, providing the foundation for the subsequent studies.[15,16] Over the years, bibliometric analysis has been employed in many health topics, including rare diseases.[17,18] Given the extensive study of BrS, a bibliometric analysis is warranted to acknowledge and celebrate those contributing to this important part of channelopathies research. This study aimed at exploring hotspot evolution and frontier of the BrS field by analyzing scientific literature from 2002 to 2022, to provide new visions for future researchers and clinical workers, especially for those who have curiosity but are novices in this field.

2. Materials and methods

2.1. Data collection

All scientific literature was retrieved from the Science Citation Index Expanded of the Web of Science Core Collection database. According to the MeSH term, we used " Topic Search = Brugada syndrome" as the search strategy, and the search period was limited from 2002.01.01 to 2022.06.23. Only articles and review articles written in English were included. Record content selected full record and cited references. The records were exported as plain text files and saved in the format of download. txt. The entire process was conducted within 1 day (June 23, 2022) to reduce the bias associated with database updating.

2.2. Data analysis

The number of publications (Np) and citations without self-citations (Nc) are 2 main bibliometric indicators for judging academic success. In general, Np is used to measure productivity, and Nc is the yardstick of scientific impact. The *h*-index is a research-level metric that evaluates both the productivity and citation impact of the publications by finding the threshold that connects Np with Nc. It is defined as the maximum value of *h* so that the given scholar has published at least *h* papers that have each been cited no less than *h* times.[19] The index has more recently been applied to the productivity and impact of a journal as well as an institution or a country.[20] Besides, the impact factor obtained from the latest 2021 Journal Citation Reports can be used as a proxy for the relative importance of a journal within its field.[21]

Relevant data were imported into CiteSpace and VOSviewer to perform visual analysis. CiteSpace version 6.1.R2 (Drexel University, Philadelphia, PA) was applied to analyze the contribution and cooperative relationship analysis. Developed by Chen,[22] Citespace is a tool for progressive knowledge domain visualization. It is particularly applicable for analyzing and visualizing patterns and trends in scientific literature. The main objective of knowledge domain visualization is to find key points in the development of research. CiteSpace provides a visual aid that characterizes the research hotspots and evolution processes, as well as forecasts the future trends of the domain intuitively.[13,23] VOSviewer version 1.6.18 (Leiden University, Leiden, Netherlands) was used to illustrate the keyword co-occurrence analysis. Unlike the conventional tools for constructing and viewing bibliometric networks, VOSviewer focuses on the graphic representation of knowledge mappings. It is ideal for sizable bibliometrics display in an easy-to-explain way.[14] Scimago Graphica was also involved for a more precise presentation of the analysis.

3. Quantitative analysis of basic information

3.1. Analysis of publications distribution

As shown in Figure 1, the publication outputs and citations concerning BrS demonstrated an overall upward trend. From 2002 to 2022, 3042 BrS-themed publications (including 2464 articles and 578 review articles) were issued on Web of Science Core Collection. The total citations without self-citations were 58,440, and the average number of citations was 30.93 per item. The *h*-index of all papers was 133. 2018 and 2021 were the 2 most productive years with 208 and 206 published papers, respectively.

Five hundred and thirty-seven academic journals were involved in the BrS research. The top 10 productive journals are listed in Table 1. Five journals had more than 100 papers, and *Heart Rhythm* ranked first (Np = 227, Nc = 9151, *h*-index = 55). Although *Circulation* preserved 90 publications, it had the highest citations, *h*-index, and impact factor (Nc = 15,510, *h*-index = 66, impact factor = 39.918). *Journals of the American College of Cardiology* had the second high impact factor (27.203). The number of times that a journal is co-cited, is an important scientific metric to measure whether it has a considerable impact in the domain. Five journals had been co-cited more than 5000 times. Again, *Circulation*, *Journals of the American College of Cardiology*, and *Heart Rhythm* were the top 3 in co-citations. Nearly all the top 10 journals and co-cited journals belong to Q1 or Q2, based on the latest Journal Citation Reports in 2021.

3.2. Analysis of contribution and cooperative relationship

During 2002 to 2022, 82 countries, 2689 institutions, and 10,952 authors were involved in the BrS research. The top 10 high-output countries and their cooperation are presented in Figure 2. As shown in Table 2, the USA employed the highest number of papers (Np = 910, 29.91%), far above second-ranked Japan (Np = 512, 16.83%) and third-ranked Italy (Np = 340, 11.18%). The USA also received the highest citations (Nc = 38,817) and *h*-index (110). Notably, the Netherlands had the second-best metrics (Nc = 16,618, *h*-index = 75) with only 288 papers.

The top 10 productive institutions and institutional cooperation are demonstrated in Figure 3B. As depicted in Table 3, the University of Amsterdam had the highest outputs, citations, and *h*-index (Np = 183, Nc = 14,440, *h*-index = 70), followed by Masonic Medical Research Institute (Np = 119, Nc = 11,304, *h*-index = 54). Betweenness centrality (BC) measures the strength of the connection between a node and other nodes.[24] CHU de Nantes and the University of Pavia had a high BC (>0.1), as indicated by the node's purple trims in Figure 3A. Such nodes tend to have more influence and bridge different entities within the domain.

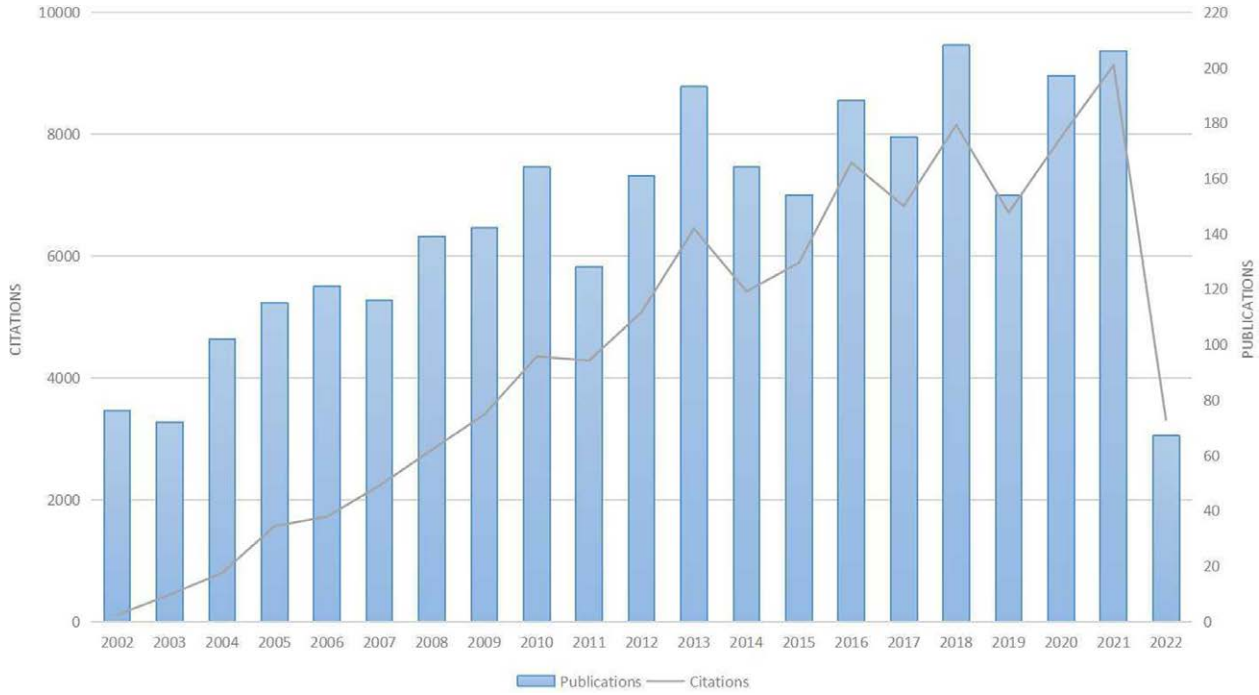

Figure 1. Trends of BrS-themed publications over the past 20 years. BrS = Brugada syndrome.

Table 1

Top 10 journals and co-cited journals related to BrS (2002–2022).

No	Journal	Np	*h*-index	Nc	IF	JCR	Journal	Nc	IF	JCR
1	Heart Rhythm	227	55	9151	6.779	Q1	Circulation	1,8409	39.918	Q1
2	Europace	139	28	2464	5.486	Q2	JACC	9529	27.203	Q1
3	JCE	132	33	3391	–	–	Heart Rhythm	8200	6.779	Q1
4	J Electrocardiol	129	18	1633	1.38	Q4	JCE	5547	–	–
5	PACE	114	22	1785	1.976	Q3	Circ Res	5068	23.213	Q1
6	Circulation	90	66	15,510	39.918	Q1	Eur Heart J	3726	35.855	Q1
7	ANE	86	17	964	1.485	Q4	Cardiovasc Res	2895	13.081	Q1
8	Circ J	82	24	1608	3.35	Q3	Circ Arrhythm Electrophysiol	2715	6.568	Q1
9	Circ Arrhythm Electrophysiol	78	33	3431	6.568	Q1	NEJM	2593	176.079	Q1
10	JACC	74	19	1598	27.203	Q1	Europace	2413	5.486	Q2

ANE = Annals of Noninvasive Electrocardiology, BrS = Brugada syndrome, IF = impact factor, JACC = Journal of the American College of Cardiology, JCE = Journal of Cardiovascular Electrophysiology, JCR = Journal Citation Reports, Nc = citations without self-citations, NEJM = New England Journal of Medicine, PACE = Pacing and Clinical Electrophysiology.

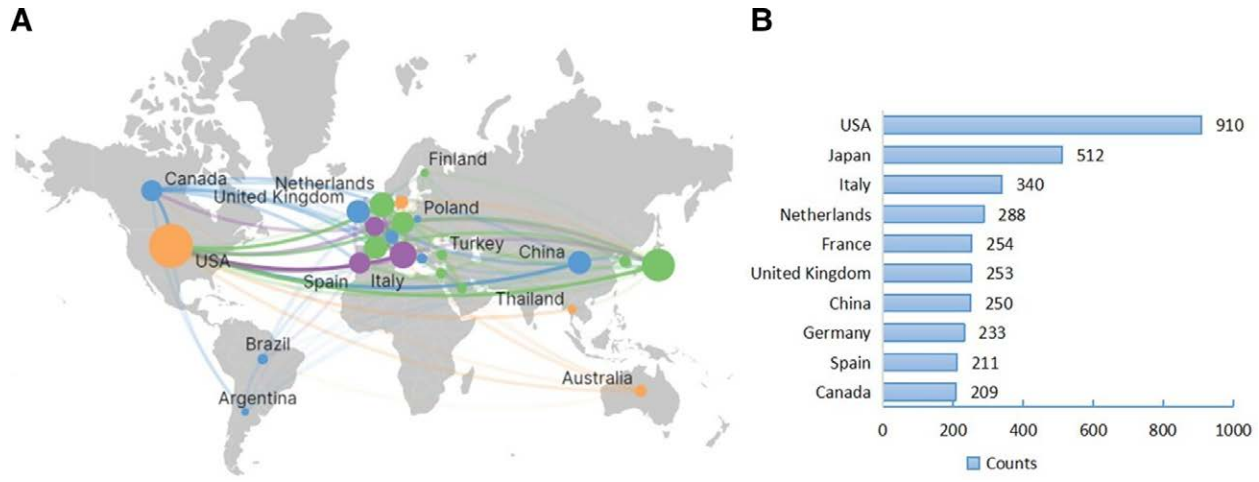

Figure 2. Country collaboration network (A) and top 10 countries (B) in BrS research (2002–2022). BrS = Brugada syndrome.

Table 2

Top 10 countries/regions for publications and centrality in the field of BrS (2002–2022).

Rank	Country/region	Np (% of 3042)	Nc	*h*-index	Country/region	BC
1	USA	910 (29.91%)	38,817	110	USA	0.28
2	Japan	512 (16.83%)	15,035	62	United Kingdom	0.2
3	Italy	340 (11.18%)	14,376	62	Spain	0.2
4	Netherlands	288 (9.47%)	16,618	75	France	0.16
5	France	254 (8.35%)	13,278	59	Germany	0.15
6	United Kingdom	253 (8.32%)	7661	46	Italy	0.13
7	China	250 (8.22%)	3931	33	Canada	0.13
8	Germany	233 (7.66%)	13,774	56	Denmark	0.12
9	Spain	211 (6.94%)	9566	48	South Africa	0.11
10	Canada	209 (6.87%)	6732	43	Switzerland	0.1

BC = betweenness centrality, BrS = Brugada syndrome, Nc = citations without self-citations, Np = number of publications.

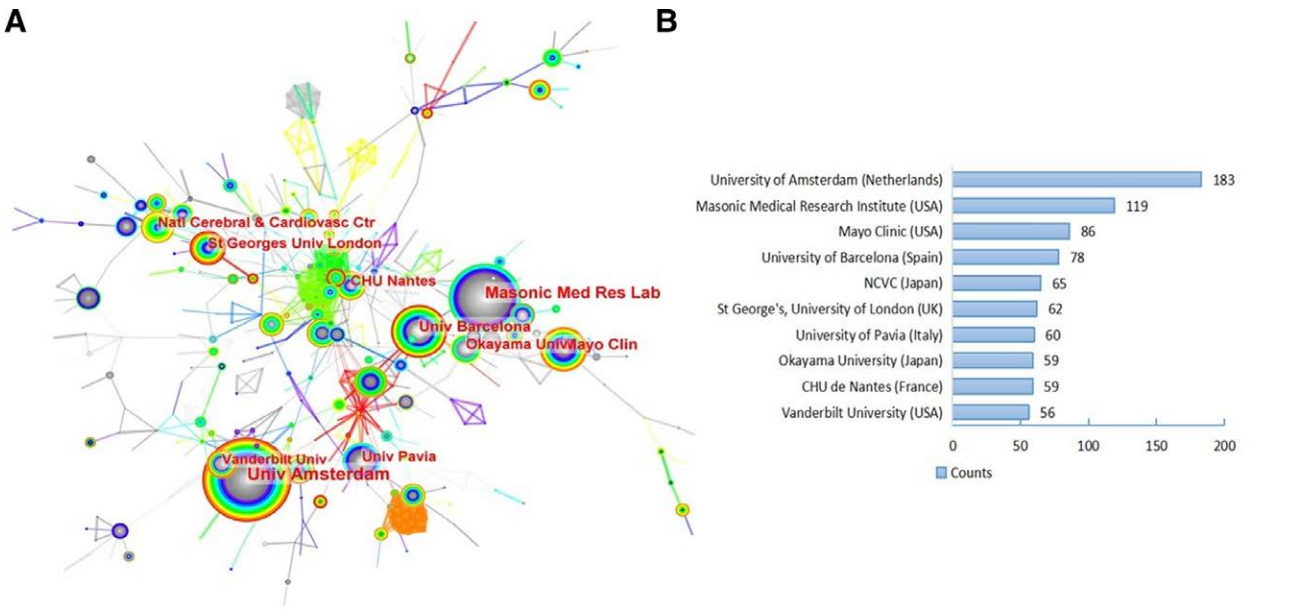

Figure 3. Institution collaboration network (A) and top 10 Institutions (B) in BrS research (2002–2022). BrS = Brugada syndrome.

Table 3

Top 10 institutions for publications and betweenness centrality in the field of BrS (2002–2022).

No.	Institutions	Country	Np	Nc	*h*-index	Institutions	BC
1	Univ Amsterdam	Netherlands	183	14,440	70	CHU Nantes	0.17
2	MMRI	USA	119	11,304	54	Univ Pavia	0.13
3	Mayo Clin	USA	86	6108	45	Univ Amsterdam	0.1
4	Univ Barcelona	Spain	78	7276	40	MMRI	0.1
5	NCVC	Japan	65	5775	37	NYU	0.09
6	SGUL	England	62	2436	27	Univ Barcelona	0.08
7	Univ Pavia	Italy	60	6101	39	Lankenau Med Ctr	0.07
8	Okayama Univ	Japan	59	2976	30	Mayo Clin	0.06
9	CHU Nantes	France	59	8679	41	Vanderbilt Univ	0.06
9	Vanderbilt Univ	USA	56	4811	34	INSERM	0.06

BC = betweenness centrality, BrS = Brugada syndrome, INSERM = French National Institute of Health and Medical Research (French: Institut national de la santé et de la recherche médicale), MMRI = Masonic Medical Research Institute, Nc = citations without self-citations, NCVC = National Cerebral and Cardiovascular Center, Np = number of publications, NYU = New York University, SGUL = St George's, University of London.

The top 10 prolific authors and their collaboration network are illustrated in Figure 4B. Table 4 also lists the top 10 highly cited authors and co-cited authors. Pedro Bugada had the highest number of published papers (Np = 135). Besides, Author Wilde, Charles Antzelevitch, Ramon Brugada, and Joseph Brugada published more than 100 papers. As for the citations and *h*-index, Author Wilde (Nc = 5635, *h*-index = 56) and Charles Antzelevitch (Nc = 5477, *h*-index = 55) were much higher than other scholars. There were some obvious collaboration networks as shown in Figure 4A, such as the Brugadas, Charles Antzelevitch and Wataru Schimizu, Author Wilde, Frederic Sacher and Connie Bezzina. Those authors also had

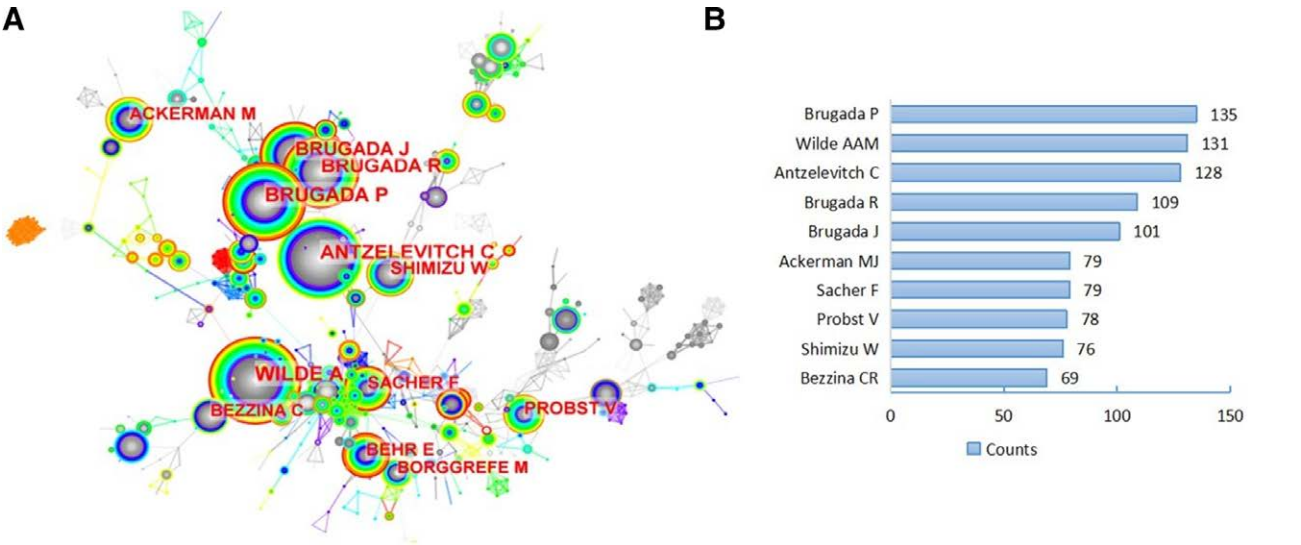

Figure 4. Author collaboration network (A) and top 10 authors (B) in BrS research (2002–2022). BrS = Brugada syndrome.

Table 4

Top 10 authors, cited authors, and co-cited authors of BrS (2002–2022).

No.	Author	Np	*h*-index	BC	Cited author	Nc	Co-cited author	Nc
1	Brugada P	135	40	0.06	Wilde AAM	5635	Antzelevitch C	3025
2	Wilde AAM	131	56	0.05	Antzelevitch C	5477	Priori SG	2754
3	Antzelevitch C	128	55	0.04	Ackerman MJ	4232	Brugada P	1592
3	Brugada R	109	40	0.02	Borggrefe M	2847	Brugada J	1100
3	Brugada J	101	40	0.03	Brugada P	2782	Schwartz PJ	1046
6	Ackerman MJ	79	45	0.03	Brugada R	2614	Wilde AAM	929
6	Sacher F	79	30	0.06	Brugada J	2594	Yan GX	841
8	Probst V	78	35	0.01	Probst V	2514	Shimizu W	795
8	Shimizu W	76	35	0.06	Tan HL	2478	Probst V	715
10	Bezzina CR	69	37	0.02	Shimizu W	2468	Morita H	698

BC = betweenness centrality, BrS = Brugada syndrome, Nc = citations without self-citations, Np = number of publications.

relatively high BC, which implies that they had more impact on others' work and studies from other groups. Two authors are considered as being co-cited when one or more papers from each author's oeuvre occur in the same reference list.[25] Five authors had a co-citation frequency of more than 1000 times. Charles Antzelevitch (3025) was the most frequently co-cited author, followed by Silvia Priori (2754).

4. Analysis of hotspots and frontiers

4.1. Keyword analysis

Keyword analysis can effectively track research hotspots and predict developmental trends.[22] There were 6186 keywords in 3042 papers, among which 16 keywords appeared more than 200 times, and 45 keywords occurred 100 times or above. Figure 5 shows the keyword co-occurrence, clustering, density distribution (Fig. 5C), and top 20 keywords (Fig. 5D). As shown in Figure 5A, Brugada syndrome (2308), ST-segment elevation (986), sudden cardiac death (784), and long QT syndrome (674) were keywords with the biggest nodes, highest density, and frequency, which are consistent with the theme of our study. As for the other keywords, some are signs and symptoms like arrhythmia (556) and VF (539). Some are associated with mechanisms and pathophysiology of BrS, such as mutation (445), *SCN5A* (306), genetics (238), cellular basis (178). Bundle branch block (652) and electrocardiogram (229) belong to medical diagnosis. Besides, risk stratification (362) is critical in previous management. Descriptive terms such as sudden death, death, prevalence, and risk, correspond to scholars' concerns about different aspects of BrS, which reflect the severity and complexity of this disease more or less.

Keyword clustering is combining similar, relevant queries into groups and using whole groups instead of separate keywords, which helps reflect knowledge core structure. Co-occuring keywords concerning BrS can be divided into 10 main clusters (Fig. 5B). Most clusters were associated with disease's causes or genetics, including #3 genome wide association, #4 $Na_V1.5$ channel, #5 deletion, #6 sodium channel, and #8 potassium channel. #0 long qt syndrome, #2 torsade de pointe, and #7 idiopathic VF correlated to signs and symptoms of BrS. #1 risk stratification and #9 ecg were management modalities and diagnosis methods for BrS, respectively.

Keywords with the strongest citation bursts appear frequently over a period of time and can reflect the research hotspots and their evolution in the corresponding duration. Table 5 sorts out the burst keywords within the BrS field from 2002 to 2022. In addition to the keywords mentioned above, more terms on various aspects of BrS were unveiled. Heart disease (2002–2006), cellular basis (2004–2010), early repolarization (2011–2016), registry (2015–2018), and guideline (2018–2022) all have high strength (>5), implying that they were among the hot topics during the different stages of the BrS research.

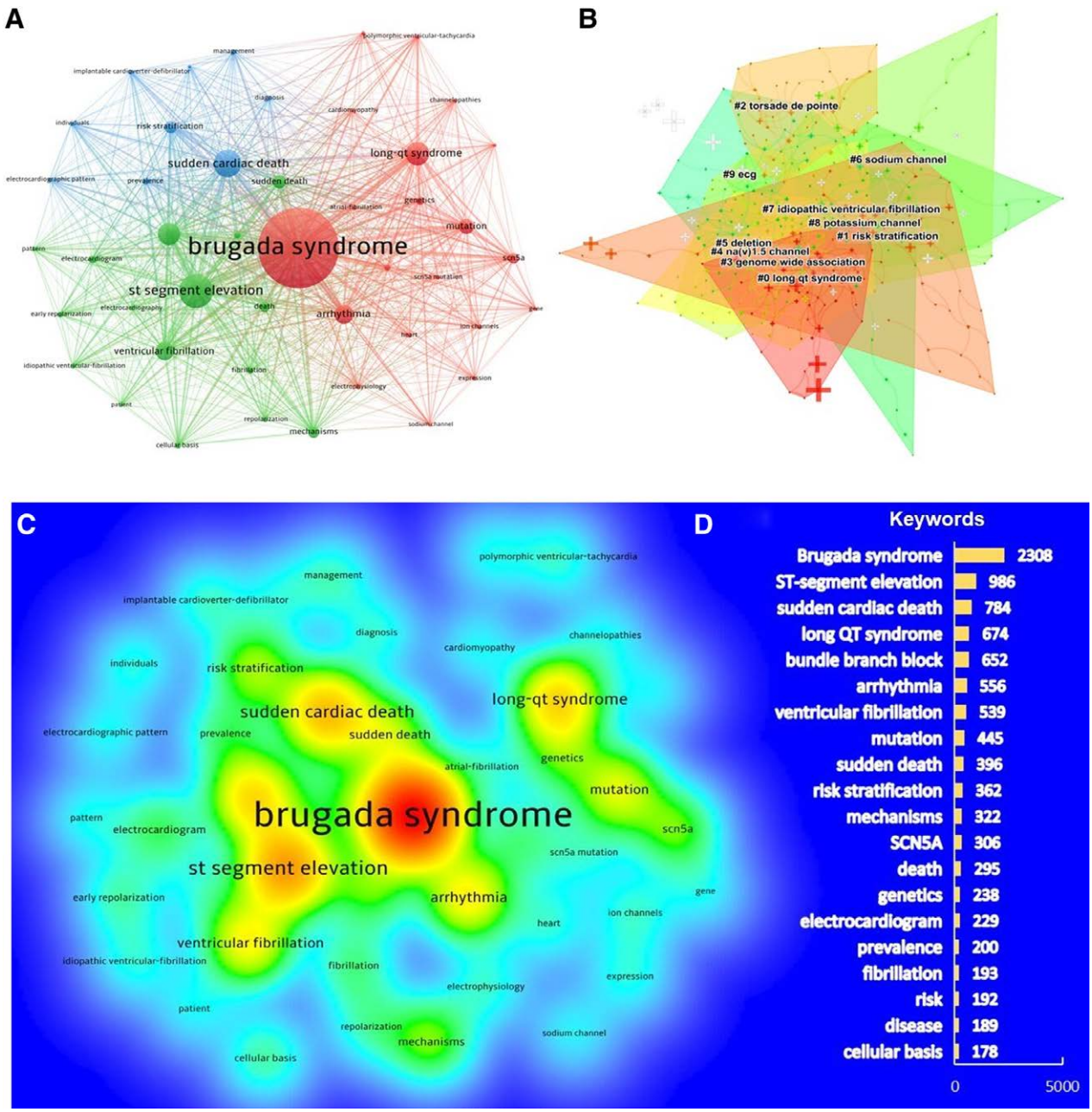

Figure 5. Keyword co-occurrence (A), clustering (B), keyword density map (C), and top 20 keywords (D) in the field of BrS (2002–2022). BrS = Brugada syndrome.

4.2. Co-citation analysis

Co-citation analysis can identify patterns and trends regarding the structure and dynamics of the underlying scientific literature. A citation refers to the fact that article A refers to an existing article B. A is known as the citing article, and B is called the cited reference. Co-citations refer to the fact that 2 references are cited simultaneously by the third article. The collection of co-cited references is the foundation of a discipline, while the citing articles represent the research frontiers. Co-citation clustering is determined by the terms extracted from the citing articles, which can be regarded as the research frontiers. As depicted in Figure 6, there are 11 co-citation clusters, and the largest 3 clusters are: #0 expert consensus statement, #1 genetic testing, #2 sudden unexplained nocturnal death syndrome. Among the 41,303 co-cited references retrieved, Table 6 lists the 10 most frequently cited references, of which an expert consensus statement published in *Circulation* by Antzelevitch et al[26] in 2005 had the highest citations.

Based on the statistical and visual analysis, we summarize the key documents and innovative findings that have advanced the discipline in chronological order and citation frequency. Publications from journals like *Circulation*, *Journals of Molecular and Cellular Cardiology*, *New England Journal of Medicine*, and *Journals of the American College of Cardiology* were mainly analyzed to ensure research quality. According to the research content, these highly-cited papers can be classified into 4 categories: pathophysiology, diagnosis, risk stratification, and management.

4.2.1. Genetics and pathophysiology. As a heterogenous genetic disease, BrS is caused by mutations that influence the sodium current or other ionic currents. In 1998, Chen et al[8] identified the first pathogenic variant in association with BrS

Table 5

Top 25 keywords with the strongest citation bursts in BrS research (2002–2022).

Keywords	Strength	Begin	End	2002–2022
bundle branch block	51.34	2002	2007	
ST-segment elevation	26.29	2002	2007	
mechanism	26.16	2002	2007	
management	25.24	2017	2022	
right precordial lead	16.11	2002	2007	
guideline	15.75	2018	2022	
sudden death	14.94	2002	2006	
early repolarization	14.87	2011	2016	
electrocardiographic pattern	13.86	2005	2011	
ventricular arrhythmia	12.02	2018	2022	
variant	11.97	2014	2020	
catheter ablation	11.73	2017	2022	
sodium channel blocker	11.35	2002	2010	
death-sudden	11.23	2002	2008	
genetics	11.08	2018	2022	
consensus conference	9.72	2018	2022	
substrate	9.53	2016	2022	
ion channel	9.29	2005	2006	
cellular basis	9.25	2004	2010	
heart disease	9.07	2002	2006	
expert consensus statement	9	2014	2022	
programmed electrical stimulation	8.81	2015	2022	
molecular mechanism	8.75	2002	2011	
registry	8.7	2015	2018	
arrhythmic event	8.3	2018	2022	

BrS = Brugada syndrome.

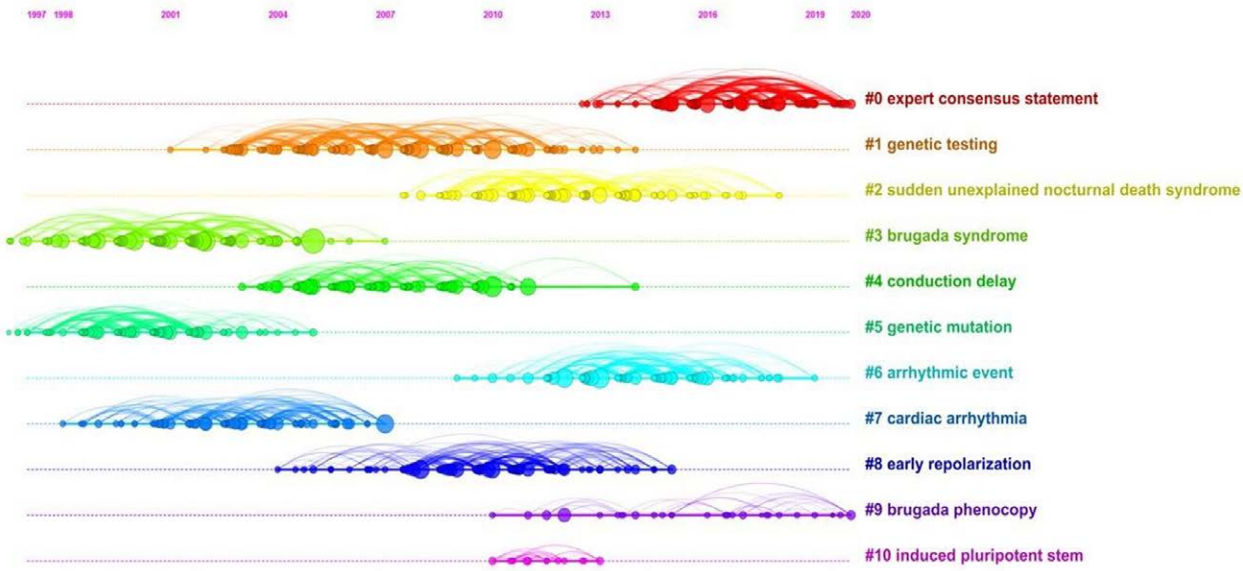

Figure 6. Timeline and cluster view of co-citation analysis in the field of BrS (2002–2022). BrS = Brugada syndrome.

in the *SCN5A* gene ($Na_V1.5$, BrS1). In a 2018 review by Wilde et al,[27] this gene encodes cardiac sodium channel Nav1.5, which is responsible for phase 0 of the cardiac action potential. *SCN5A* mutations, classified as BrS 1 type, result in loss of function of the sodium channel. In 2010, Kapplinger et al[28] performed a retrospective analysis of 2111 patients who were referred for BrS genetic testing and added 200 novel *SCN5A* mutations. Of note, they demonstrated that an identifiable *SCN5A* variant is found only in ~20% of BrS patients. Several pathogenic variants associated with BrS have been identified in other genes and altogether may be responsible for 2%~5% of diagnosed cases, according to a recent review by Brugada et al.[11] Some are responsible for other sodium channel, including *SCN1B* ($Na_V\beta1$, BrS5),[29] *SCN2B* ($Na_V\beta2$, BrS14),[30] *SCN3B* ($Na_V\beta3$, BrS7),[31] and *SCN10A* ($Na_V1.8$, BrS17).[32] Some genes encode ion channels that carry calcium or potassium ions. The representative fundings include *CACNA1C* (Cav1.2, BrS3) and *CACNB2b* (Cavβ2b, BrS4) by Antzelevitch et al in 2007.[33] In 2008, Deplón et al[34] first described *KCNE3* (MiRP2, BrS6) which regulates the potassium channel I_{to} associated with BrS. Others generate proteins that interact with ion channels, like *GPD1-L* (BrS2) reported by London in 2007. A *GPD1-L* mutation may decrease cardiac Na^+ current and causes BrS.[35] Through a genome-wide association study, Bezzina et al[36] detected 3 alleles comprising *SCN5A*, *SCN10A*, and *HEY2* (BrS18) which solitarily increased BrS risk, as well as additively.

The underlying mechanism of BrS remains a subject of debate. Currently, there are 2 leading hypotheses. In a scholarly debate,

Table 6

The top 10 co-cited references concerning BrS (2002–2022).

No.	Cited references	Citation
1	Antzelevitch C, 2005, CIRCULATION, Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association	234
2	Priori SG, 2013, HEART RHYTHM, HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes	159
3	Priori SG, 2002, CIRCULATION, Natural history of Brugada syndrome: insights for risk stratification and management	152
4	Probst V, 2010, CIRCULATION, Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry	142
5	Priori SG, 2012, JACC, Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry	125
6	Wilde AAM, 2002, CIRCULATION, Proposed diagnostic criteria for the Brugada syndrome: consensus report	125
7	Brugada J, 2002, CIRCULATION, Long-Term Follow-Up of Individuals With the Electrocardiographic Pattern of Right Bundle-Branch Block and ST-Segment Elevation in Precordial Leads V_1 to V_3	123
8	Brugada R, 2000, CIRCULATION, Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts	121
9	Antzelevitch C, 2007, CIRCULATION, Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death	117
10	Haissaguerre M, 2008, NEJM, Sudden Cardiac Arrest Associated with Early Repolarization	116

BrS = Brugada syndrome.

Wilde et al[37] addressed that depolarization disorder forms the basis of the BrS. The depolarization hypothesis relies on abnormally slow conduction in the right ventricle and cardiac structural changes. On the contrary, Antzelevitch et al argued the repolarization hypothesis as the predominant mechanism underlying BrS. The repolarization hypothesis relies on transmural dispersion of repolarization between the endocardium and epicardium of the right ventricle outflow tract. As BrS can be caused by mutations in various genes, different mechanisms may bear the responsibility for the arrhythmias seen in different patients.

4.2.2. Diagnosis. Current In 2002, Wilde et al[38] proposed the first proper diagnostic criteria for BrS through ESC consensus documents. Adjusted guidelines were reported in 2005[26] and 2013[39] till Shangai criteria in 2016[40] and the last review was made by Brugada et al in 2018.[11] Until 2013, BrS diagnosis recommended both the presence of type 1 ECG pattern and clinical manifestations. However, because many individuals with type 1 ECG are asymptomatic, the 2013 consensus statement required no further evidence of malignant arrhythmias.[41] Previous guidelines did not invlove additional criteria for patients with drug-induced type 1 ECG, thereby possibly overdiagnosing BrS. Hence, the recent Shanghai citeria includes additional information to make a definite diagnosis.

4.2.3. Risk stratification. After the diagnosis, the number one issue is mainly associated with the patient's outcome and prognosis. Risk stratification in BrS patients, influenced by various clinical, ECG, and electrophysiological factors, aims to identify those with a greater likelihood of serious arrhythmic events. In 2002, Pedro and Josep Brugada first analyzed the long-term follow-up data of BrS patients (N = 334). They proposed that inducibility VAs and type 1 ECG are predictors of arrhythmia occurrence.[42] In the same year, Priori et al[43] failed to corroborate a utility for VAs inducibility at programmed electrical stimulation in their BrS cohort (N = 200). In contrast, they demonstrated that the presence of a spontaneous type 1 ECG combined with the history of cardiogenic syncope has the greatest impact on serious arrhythmic events; accordingly, they proposed a risk stratification scheme that recommends ICD only in patients with these manifestations. In 2010, this prospective evaluation was confirmed by Probst et al[44] in a long-term prognosis involving 1029 BrS patients from 4 European countries (FINGER registry). They also found that patient age and sex are not predictive of arrhythmic events. In 2012, the PRELUDE cohort (N = 208) identified 2 novel predictors of life-threatening events: the presence of QRS fragmentation and short ventricular refractory period.[45] Recent evidences showed that conduction abnormalities may also play a role in the risk stratification in Brugada patients. In 2019, Migliore et al[46] first demonstrated that first-degreee atrioventricular block is an independent predictor of life-threatening arrhythmic events, as well as a stronger marker of arrhythmic risk than a spontaneous ECG changes. According to their recent study, S-wave in lead I on basal ECG is the only independent predictor of persistent risk of malignant arrhythmic events.[47] Therefore, these easily obtainable ECG markers should be considered in designing clinical algorithm for individual risk assessment in BrS. Overall, the presence of spontaneously diagnostic BrS ECG, cardiogenic syncope, conduction abnormalities, along with consideration for undertaking programmed electrical stimulation have been identified as risk markers for future events.

4.2..4. Management. The main aim when treating BrS patients is to reduce the risk of SCD due to malignant arrhythmias. In the 2013 HRS/EHRA/APHRS consensus statement, the first line of treatment, suitable for all BrS patients, is lifestyle changes.[39] These include avoiding substances that may increase the risk of serious arrhythmias, such as excessive alcohol and certain medications, and treating fever rapidly with antipyretics. Postema et al[48] provided a list of drugs that are contraindicated in BrS. An ICD should always be implanted in symptomatic patients for the prevention of VAs and SCD, according to the recommendations of the international consensus and guidelines.[41] In a cohort with 60 BrS patients, Belhassen et al[49] reported that quinidine, an antiarrhythmic drug, is useful in the pharmacologic management of BrS. Arrhythmic events occurred in only 2 cardiac arrest survivors treated with ICD alone but did not recur on quinidine. A further treatment option is a radiofrequency ablation. Pappone et al[49] demonstrated that arrhythmogenic electrophysiological substrate elimination by radiofrequency ablation results in ECG normalization and ventricular tachycardia/VF noninducibility, in 133/135 (98.5%) patients during a median follow-up of 10 months.

5. Emerging trends

We explore the emerging trends in the BrS field by analyzing burst keywords and references during the past 3 years

Table 7

The emerging burst keywords in the field of BrS (2019–2022).

Keywords	Strength	Begin	End	2002–2022
event	6.03	2019	2022	
sudden cardiac arrest	5.62	2019	2022	
association	5.03	2019	2022	
sudden cardiac death	4.59	2019	2022	
outcome	3.48	2020	2022	
exercise	3.39	2019	2022	
cardioverter defibrillator	3.34	2019	2022	
common variant	3.24	2019	2022	
J wave syndrome	3.19	2020	2022	
cardiac channelopathy	3.18	2019	2022	
wave	3.18	2019	2022	

BrS = Brugada syndrome.

Table 8

Top 10 references with the strongest citation bursts concerning BrS (2019–2022).

No.	References	Strength	2002–2022
1	Yan Z, 2017, CELL, Structure of the Nav1. 4-β1 complex from electric eel	1.82	
2	Priori SG, 2013, HEART RHYTHM, HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes	1.82	
3	Bagnall RD, 2016, NEJM, A Prospective Study of Sudden Cardiac Death among Children and Young Adults	1.48	
4	Johnson CN, 2018, STRUCTURE, A Mechanism of Calmodulin Modulation of the Human Cardiac Sodium Channel	1.21	
5	Portero V, 2018, FRONT PHYSIOL, KV4.3 Expression Modulates NaV1.5 Sodium Current	1.21	
6	Clatot JM, 2020, INT J MOL SCI, Inter-Regulation of Kv4.3 and Voltage-Gated Sodium Channels Underlies Predisposition to Cardiac and Neuronal Channelopathies	1.21	
7	James CA, 2013, JACC, Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy–Associated Desmosomal Mutation Carriers	1.21	
8	Zorzi A, 2016, CIRC-ARRHYTHMIA ELEC, Nonischemic Left Ventricular Scar as a Substrate of Life-Threatening Ventricular Arrhythmias and Sudden Cardiac Death in Competitive Athletes	1.21	
9	Finocchiaro G, 2016, JACC, Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry	1.21	
10	Corrado D, 2017, NEJM, Arrhythmogenic Right Ventricular Cardiomyopathy	1.21	

Red line represents burst time and blue line represents publication time.

BrS = Brugada syndrome.

(2019–2022). As shown in Table 7, some keywords are outcomes of BrS: "event," "sudden cardiac arrest," and "sudden cardiac death." Some are novel pathologic concepts: "common variant," "J wave syndrome," and "cardiac channelopathy." Others like "exercise" and "cardioverter defibrillator" involve management of BrS. These keywords might be the hotspots for current and future BrS research.

For further analysis, we selected recent references with the strongest citation bursts (Table 8). Half of the papers focused on the pathophysiology associated with BrS, especially the structure and function of the cardiac sodium channel. Further investigation into this concept would enrich the understanding of the underlying pathophysiology of BrS and may give rise to future exploration of the targeted therapy. The other studies deal with SCD among youngsters and athletes. These findings highlight the need for complementary preventive strategies. Specifically, the 2013 HRS/EHRA/APHRS expert consensus statement by Priori et al appeared again on this list, which summarized the clinical guidelines for diagnosis, risk stratification, and management of BrS patients. This document has considerably improved the care of BrS patients. Based on the references above, we note that the pathophysiological basis of BrS is incompletely understood. However, the progress in the understanding of BrS has been steady, and the future of BrS patients looks very promising. In summary, the underlying pathophysiological mechanisms (especially the ion channel abnormality and related genetic basis), the development of novel therapies, and personalized risk assessment for different populations might be the emerging trends of BrS research.

6. Discussion

In this study, we conducted a bibliometric analysis to explore the research hotspots and developmental trends of BrS. Firstly, general information (i.e., the annual publications, authors, institutions, countries, and journals) was quantitatively analyzed. BrS is a progressively developing research field with an increase in publications over time, due to the enhanced recognition of this entity. The top 10 institutions and authors were concentrated in the USA and European countries, indicating their outstanding contributions to BrS advancement. Second, we obtained the research hotspots in BrS by analyzing the keywords and citations. Notably, we focused our analysis on highly cited publications from influential journals and identified the dynamic evolutions of research hotspots in the pathophysiology, diagnosis, risk stratification, and management of BrS. Finally, we highlighted several emerging trends by visualizing BrS-themed publications and keywords during the past 3 years. However, there were some limitations in our study. Firstly, the database is updated continuously and dynamically. Hence, our results are essentially temporary and

by default will not incorporate ongoing and future research areas. Secondly, only English publications from Science Citation Index-expanded databases were included. Therefore, a discrepancy may exist between our analysis and the real publication characteristics.

Overall, BrS remains a challenging disease entity. Its underlying pathophysiological mechanisms remain to be elucidated. Perhaps the polygenic factors are important for both the phenotypic expression of BrS and clinical outcomes. These variables lead to the present uncertainty and difficulty in making the correct diagnosis, risk stratification, and management. Hence then, physicians should assess patients with definite or possible BrS to implement personalized therapies, with the help of current BrS guidelines.

7. Conclusion

This bibliometric analysis reveals that the BrS research is prosperous during the past 20 years. The USA, Japan, and some European countries like the Netherlands had made many outstanding breakthroughs in this field. The vast majority of articles concerning BrS were published and cited in influential scientific journals. Among them, *Circulation*, *Journals of the American College of Cardiology*, and *Heart Rhythm* were the 3 most representative journals. The research hotspots over the decades were pathophysiology, diagnosis, risk stratification, and management. Our results indicate that the underlying mechanisms, novel therapies, and personalized risk assessment might be the future trends of the BrS research.

Author contributions

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