Original Article

The top-100 most cited articles of biomarkers in congenital heart disease: a bibliometric analysis

Kang Yi[1,2,3#], Jian-Guo Xu[1#], Ke-Lu Yang[4], Xin Zhang[3,5], Long Ma[5], Tao You[2,3], Jin-Hui Tian[1,3,6]

[1]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, China; [2]Department of Cardiovascular Surgery, Gansu Provincial Hospital, Lanzhou, China; [3]Gansu International Scientific and Technological Cooperation Base of Diagnosis and Treatment of Congenital Heart Disease, Lanzhou, China; [4]Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, KU Leuven-University of Leuven, Leuven, Belgium; [5]First School of Clinical Medical of Gansu University of Chinese Medicine, Lanzhou, China; [6]Key Laboratory of Evidence Based Medicine and Knowledge Translation of Gansu Province, Lanzhou University, Lanzhou, China

Contributions: (I) Conception and design: K Yi, JG Xu, T You, JH Tian; (II) Administrative support: T You, JH Tian; (III) Provision of study materials or patients: K Yi, JG Xu, KL Yang, X Zhang; (IV) Collection and assembly of data: K Yi, JG Xu, X Zhang, L Ma; (V) Data analysis and interpretation: K Yi, JG Xu, KL Yang, X Zhang, L Ma; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Jin-Hui Tian. Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, No. 199, Donggang West Road, Lanzhou City, Gansu Province, 730000, China. Email: tjh996@163.com; Tao You. Department of Cardiovascular Surgery, Gansu Provincial Hospital, No. 204, Donggang West Road, Lanzhou 730000, China. Email: youtao2016@126.com.

Background: Biomarkers have played an important role in the treatment and management of patients with congenital heart disease (CHD). The 100 most frequently cited articles addressing the possible role of biomarkers assessment in treatment and outcomes in patients with CHD were reviewed.

Methods: The Web of Science Core Collection database was selected as the database for this selection of publications. CiteSpace 5.7.R1 and VOSviewer 1.6.9 were used to analyze the information.

Results: A total of 877 articles referencing cardiac biomarkers and CHD were identified in the search period January 1980–June 2020. After screening, the top 100 most cited articles were finally determined. These articles were published in 56 journals, of which the Pediatric Cardiology published the most articles (n=8). Countries collaboration involved a total of 10 countries, and the visualized map indicated the USA had the strongest collaboration network. Related topics of future research will still focus on prevention, general condition evaluation, surgical prognosis evaluation, and application of natriuretic peptide in CHD.

Conclusions: We conducted an insight to acquainting characteristics of highly cited publications of biomarkers in CHD and highlighting the research subjects, global research trends, and network collaboration between countries. Related topics of frontiers will focus on: (I) the application of natriuretic peptide, (II) the diagnostic and prognostic value of genes and their related transcriptional translation agents, (III) the use of biomarkers to evaluate and predict the postoperative injury caused by extracorporeal circulation, (IV) and the application of other biomarkers (such as oxidative stress, homocysteine, and thrombosis) to assess and predict damage circumstance.

Keywords: Congenital heart defect; biomarkers; bibliometric analysis; citation analysis; visualized maps

Submitted Aug 28, 2021. Accepted for publication Nov 26, 2021.
doi: 10.21037/apm-21-2422
View this article at: https://dx.doi.org/10.21037/apm-21-2422

Introduction

Congenital heart disease (CHD) is typically defined as a defect in the structure and function of the heart caused by abnormal heart development before birth. The prevalence of CHD has gradually increased from 8.2 to 9.4 cases per 1,000 live births over the past 10 years (1,2). CHD may be caused by chromosomal abnormalities, environmental factors and micronutrient deficiencies, but there remains substantial uncertainty regarding risk factors of 80% cases (3-5). Improvements in surgical practice and intervention had resulted in a significant reduction in CHD mortality (6,7). The number of deaths due to CHD in 2017 was estimated to be 261,247 (range from 216,567 to 308,159), a decrease of 34.5% from the estimated in 1990. The decline in mortality had also led to an estimated 12 million patients with CHD worldwide in 2017, an increase of 18.7% from 1990 (8). With all improvements in care, it might be predicted that adult with congenital heart disease (ACHD) will eventually grow to an estimated 75,000 patients per ten million residents (9).

With the landscape of CHD dramatically changing, the sequelae of CHD and its treatments have increasingly emerged (10). The detection of fetal CHD and evaluation of postoperative risk are the keys to reducing mortality and improve the management of CHD. The use of biomarkers have been demonstrated to provide a minimally-invasive method that can be used to monitor the basic conditions in CHD, and incorporated into daily clinical practice for risk stratification and optimize therapeutic regimens. This is the reason why biomarkers have attracted more and more attentions in recent years (11,12). The biomarker is a quantifiable and surrogate indicator that can reflect the existence or severity of a disease. Biomarkers are broadly defined as clinical observations, laboratory tests, or imaging parameters (13) that may be able to reflect the pathophysiological process of heart disease and also be able to provide meaningful information about prognosis, to help guide clinical decision-making. Biomarkers had already played an integral role in the treatment and management of patients with heart failure and coronary heart disease because of the important information the values provided (14-17). This had also prompted the enthusiasm for research of biomarkers in CHD field meanwhile clinicians start to recognize the diagnostic and prognostic significance of biomarkers in CHD patients. In the newly released 2020 ESC Guidelines for the management of ACHD, the emerging role of biomarkers in the follow-up of ACHD had also been proposed as a new concept (18).

Bibliometric analysis was used to help determine the frequency of articles cited describing CHD and biomarkers and may help to define areas for future research. Bibliometric analysis is a research method that uses mathematical or statistical methods to describe the quantity of external characteristics of literature, and then evaluates and predicts the current status and development trend of science and technology (19-21). Bibliometrics analysis mainly uses quantitative methods to analyze the metrological characteristics of papers published in a certain field. It is an emerging discipline that studies mathematical laws in literature. Co-word analysis is an important method of bibliometrics, which can be used to identify trends and hot topics. Use modern statistical technology to classify subject keywords, summarize research hotspots and research structure, which have important reference value for planning subject layout and adjusting discipline direction (22,23).

In this study, bibliometric analysis was used to reveal the top-100 cited articles of biomarkers in CHD field for the first time, in order to provide an insight on the citation frequency of top-cited articles published on biomarkers in CHD field, to help recognize the quality of the works, discoveries, and the research trends steering biomarkers in CHD field, hoping to provide a reference for future research in this field.

Methods

Database and search strategy

We conducted a highly sensitive search for publications of biomarkers in CHD using the Web of Science (WoS) Core Collection database on 4 June 2020. Articles published between January 1980 and June 2020 were searched. The search strategies were shown in *Table 1*. The 100 most frequently cited articles identified in the search were reviewed by two of the authors (one is a cardiovascular surgeon, and the other is a researcher from evidence-based medicine center) independently. After the independent screening, two researchers cross-checked and discussed the disagreements, and finally reached a consensus on whether the suspected articles should be included. No time and language limitations were implemented on the retrieval. Document Types such as meeting abstracts, news item, conference proceeding, letters to the editor, correction, and editorial material were excluded. The review of biomarkers in cardiovascular disease (CVD) involves CHD and the

Table 1 Search strategies

Set	Query
#1	TS =("congenital heart defect" OR "congenital heart disease" OR "heart abnormality" OR "congenital heart defects" OR "congenital heart diseases" OR "heart abnormalities")
#2	TS =("atrial septal defects" OR "atrial septal defect" OR "ventricular septal defect" OR "ventricular septal defects")
#3	TS =("persistent truncus arteriosus" OR "persistent ostium primum")
#4	TS =("patent ductus arteriosus" OR "scimitar syndrome" OR "anomalous pulmonary venous connection" OR "double inlet left ventricle" OR "double outlet right ventricle" OR "interrupted aortic arch")
#5	TS =(((tetralogy OR trilogy OR syndrome) AND fallot*) OR cantrell* OR "shone's")
#6	TS =(endocardial cushion defect* OR "atrioventricular canal")
#7	TS =(tricuspid atresia* OR valve atresia* OR "pulmonary atresia" OR "absent right atrioventricular connection")
#8	TS =(foramen oval* OR lutembacher* syndrome)
#9	TS =("pulmonary stenoses" OR "pulmonary stenosis" OR "pulmonary valve stenoses" OR "pulmonary valve stenosis" OR "pulmonic stenosis" OR "pulmonic stenoses" OR "pulmonary subvalvular stenosis" OR "pulmonary subvalvular stenoses" OR "bicuspid aortic valve")
#10	TS =((aortic OR aorta*) AND coarctation*)
#11	TS =(transpos* AND (arteries OR artery OR vessel*))
#12	TS =(ventricular dysplasia* OR "hypoplastic left heart syndrome" OR "left heart hypoplasia syndrome")
#13	TS =(myocardial bridging* OR crisscross heart* OR criss - cross heart*)
#14	TS =(single ventricle* OR univentricular heart*)
#15	TS =(ebstein* anomaly OR ebstein* malformation* OR "ectopia cordis")
#16	TS =(eisenmenger* AND (complex OR syndrome))
#17	TS =(biomarker OR "biologic marker" OR "biological marker" OR "serum marker" OR "clinical marker" OR "biochemical marker" OR "Immune marker" OR "molecule marker" OR biomarkers OR "biologic markers" OR "biological markers" OR "serum markers" OR "clinical markers" OR "biochemical markers" OR "immune markers" OR "molecule markers")
#18	#16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#19	#18 AND #17

review of CHD referred to biomarkers were also included. Studies on non-human subjects were also included. The citation rate was defined as the total number of citations divided by the number of years since the article was published.

For two articles with the same absolute number of citations, the literature with high citation rate will be given priority.

Data collection and statistical analysis

Two reviewers individually classified the articles via Endnote X8 for further categorization, and extracted the following data: authors, title, publication year, citation frequency, journal name, impact factor (IF), institutions of authors, country of authors, keywords, co-citation references, co-citation authors, co-citation source journals.

The Microsoft Excel 2019 was applied to analyze publication year, journals, citation frequency, countries, institutions, co-citation references, co-citation authors, and a bubble plot was created to show the relationship between publication year and citations. Furthermore, a scatter plot of IF and average citation frequency of journals was also made using Microsoft Excel. We fitted the trend line to find the relationship between IF of journals and the average citation frequency of articles published on it. The IF of journals was obtained from the 2019 Journal Citation Reports (Clarivate Analytics, 2019).

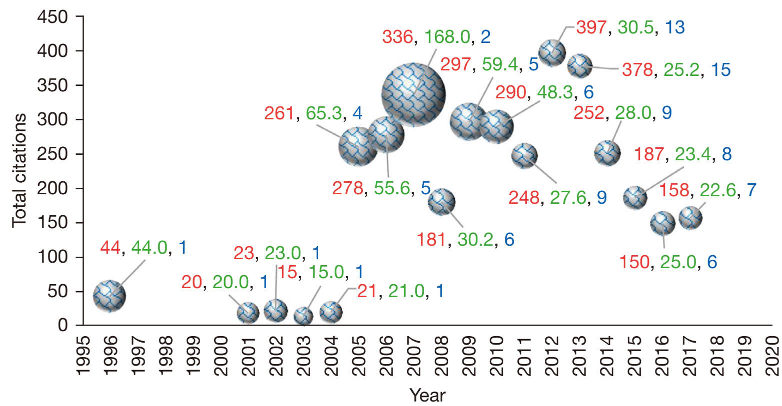

Figure 1 Bubble plot of published years and citations. Produced by Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA). In the bubble plot, the X-axis represented the time range of top 100 cited papers, the Y-axis symbolized the total amount of citations per year, the bubble size stood for the average amount of citations per article in every year. In the data label, the former (red color) is the value of total citations, the middle (green color) is the value of bubble size, and the last (blue color) is the number of papers.

Visualized analysis and network mapping

VOSviewer 1.6.9 (Leiden University, Leiden, The Netherlands) was used to extract key information, for the high frequency fields such as countries and keywords, we make a network map for visual analysis, and furthermore analyze the potential clustering (24). In cluster analysis, different colors showed different fields or directions, and represent different sub-clusters or classifications in this field. Before performing the analysis, data were standardized. We standardized different expressions about the same author or keyword into the uniform expression to reduce the bias in data analysis, and standardization was carried out manually by the authors. We also reclassified articles from England, Northern Ireland, Scotland, and Wales to the United Kingdom (UK) and articles from Hong Kong, Macau and Taiwan to China (25). CiteSpace is a scientific application for progressive knowledge domain visualization, it reveals the dynamics in scientific literature as well as visualizing and analyzing trends and patterns in a given research field (26,27). CiteSpace 5.7.R1 was used in this study to detect bursts for co-occurrence keywords and co-cited references, and design the dual-map overlay of journals. Bursts are defined as a characteristic such as author, keyword, or co-cited reference, which are cited frequently over a period of time.

Results

A total of 877 articles were reviewed and 237 have been cited more than 14 times. The selected 100 most cited related articles underwent subsequent analysis. Among the top-100 publications, 89 were original research and the remaining 11 were reviews, and the total number of citations was 3,536 while Hirsch Index was 32 (28). The authors, title, journal, and volume of the top 100 publications, as well as the citations and citation rate, were listed in available online: https://cdn.amegroups.cn/static/public/apm-21-2422-01.pdf.

Distribution of publication years

Figure 1 showed the time and citations distribution. After the identification of the 100 most frequently cited articles, the first article was published in 1996 by Taggart *et al.* (29). Compared with the previous years, the citation frequency of articles published after 2005 had increased significantly. Due to the relatively low number of citations, none of the articles published in the past three years from 2018 to 2020 ranked in the top 100. From *Figure 1*, we can also find that the average highest citations appeared in 2007, the highest total citations appeared in 2012, and most articles (n=15) published in 2013.

Sources of journals

The top 100 cited articles were published in 56 journals. *Table 2* listed the top ten contributing journals. For the complete journal list, see in Table S1. There were 28 (50%) journals from United States of America (USA), in which 56 of the 100 articles had been published. The top ten productive journals published 41 of the total number

Table 2 Journals contributed three or more papers to the top-100 cited articles

Rank	Journal	N	Cited number	Country	IF	JCR Category (SCIE)
1	*Pediatric Cardiology*	8	190	USA	1.564	Pediatrics/Cardiac & cardiovascular systems
2	*Journal of Thoracic and Cardiovascular Surgery*	5	161	USA	4.451	Respiratory system/cardiac & Cardiovascular systems/surgery
3	*International Journal of Cardiology*	5	125	Ireland	3.229	Cardiac & cardiovascular systems
4	*PLoS One*	4	125	USA	2.74	Multidisciplinary sciences
5	*American Journal of Cardiology*	4	171	USA	2.57	Cardiac & cardiovascular systems
6	*Circulation*	3	256	USA	23.603	Peripheral vascular disease/Cardiac & cardiovascular systems
7	*Heart*	3	191	UK	5.213	Cardiac & cardiovascular systems
8	*Clinical Chemistry and Laboratory Medicine*	3	89	Germany	3.595	Medical laboratory technology
9	*Pediatric Nephrology*	3	363	USA	2.676	Urology & nephrology/Pediatrics
10	*Circulation Journal*	3	84	Japan	2.54	Cardiac & cardiovascular systems

IF, Impact factor (InCites Journal Citation Reports dataset updated Jun 29, 2020); JCR, Journal Citation Reports; SCIE, Science Citation Index Expanded.

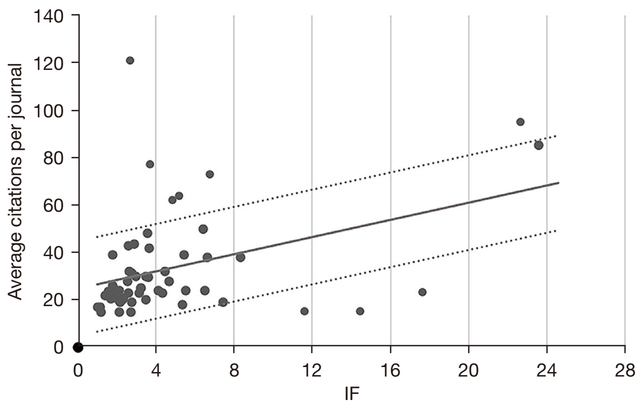

Figure 2 Scatter plot of impact factor and average amount of citations per journal. Produced by Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA). IF, impact factor.

of articles. *Pediatric Cardiology* published the largest number of papers (n=8), followed by *Journal of Thoracic and Cardiovascular Surgery* (n=5) and *International Journal of Cardiology* (n=5). Of the top ten most prolific journals in our analysis, seven were specialized journals of cardiology, one was general medical journal, one focused on biochemistry, and one focused on pediatric nephrology.

The medians (25th–75th quartiles) of IF between the 56 journals were 3.05 (2.12, 5.21). *Figure 2* showed the relationship between IF and the average amount of citations per journal. The relationship between the IF of journals and the average citations per journal was found by fitting the linear function (y =1.8074x +24.74, R^2=0.1562). We use the trend line as a benchmark, and take 20 citation frequency as the floating interval to form a range, and there were nine outlier journals outside the range.

Countries collaboration

The geographical distribution of top-100 publications of biomarkers in CHD involved 23 countries (see *Figure 3*). The USA contributed 36 articles, followed by China (n=15) and Germany (n=14). For articles completed by cooperation between different countries, this article will be included in the number of articles issued by different countries. International collaboration was analyzed based on country using the VOSviewer. *Figure 4* presented a visualization map of collaboration between different countries with minimum occurrences of three. The visualization map showed ten countries distributed in five different clusters, and each cluster with a unique color represented a close working network. The USA had the strongest collaboration network, represented by a total link strength of 13, followed by The United Kingdom (UK) (total link strength eight), Canada, and Italy (both have a total link strength of six).

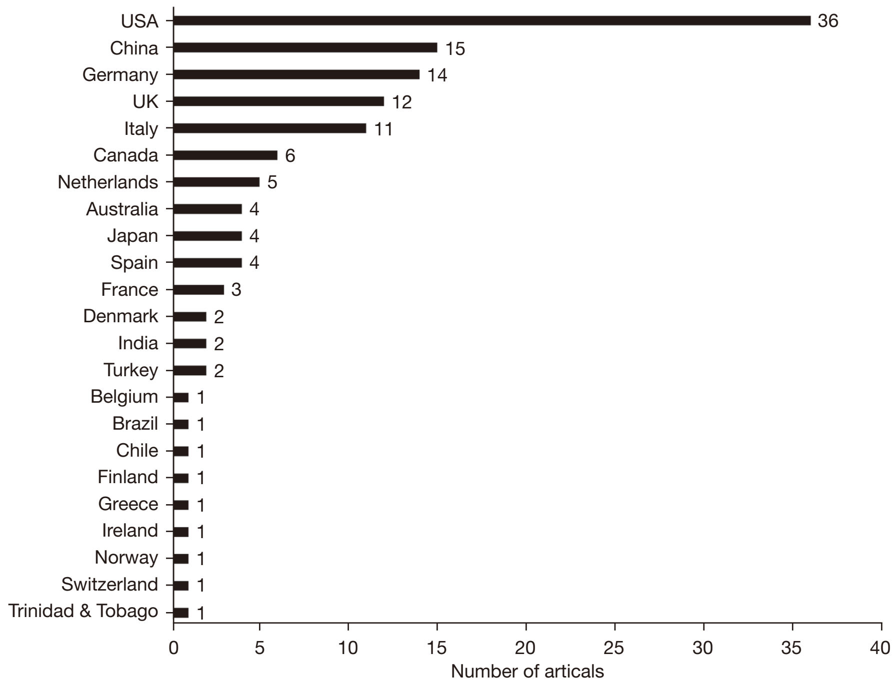

Figure 3 Countries contributed to the top-100 cited articles. Produced by Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA).

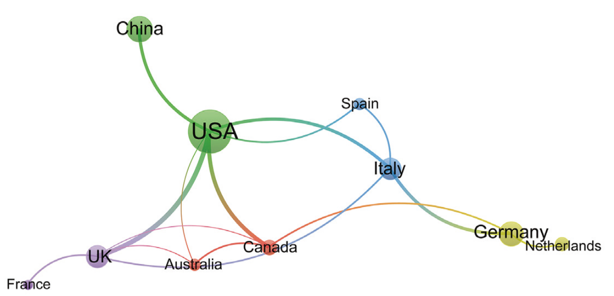

Figure 4 The network map of countries for the top 100 most cited articles on biomarkers in congenital heart disease. Produced by VOSviewer 1.6.9 (Leiden University, Leiden, The Netherlands).

Authorship/organizations collaboration

A total of 639 authors were extracted in the top-100 cited articles. The collaboration between authors is mostly limited in the same research workgroup, and the collaboration between teams was not reflected in the top 100 articles. *Table 3* showed the authors contributed to three or more papers in this field.

There was a total of 184 institutions. *Table 4* listed 11 institutions that had published three or more top-cited papers on biomarkers in CHD. The *University of Cincinnati College of Medicine* from USA and the *Fondazione Toscana G. Monasterio* from Italy were both prolific and participated in publishing 5 articles, respectively. The collaboration between institutions was the same as the collaboration between teams, and there were no obvious connections to conform a network map (see in Figure S1).

Co-citation analysis

Co-citation analysis showed a total of 21 authors had at least ten citations (0.86% of all the authors in the field). There were three articles co-cited up to ten times. The most cited publication with a citation count of 12 which was published by *Lancet* (30). The five journals which total citation frequency higher than 100 times were *Circulation* (n=241), *Journal of The American College of Cardiology* (n=137), *Journal of Thoracic and Cardiovascular Surgery* (n=123), *American Journal of Cardiology* (n=108), and *Pediatric Cardiology* (n=103), respectively. In CiteSpace, the threshold was set to top 80 in a one-year slice, strong citation bursts of co-cited references were not detected. *Figure 5* showed the dual-map overlay of journals. The left side represented the map of citing journals and the right side represented the map of cited journals. The label represented the subject covered by the journal. Colored

Table 3 The authors contributed three or more to top 100 cited articles on biomarkers in congenital heart disease

Author	Institution	N	Citations
Devarajan P	Cincinnati Children's Hospital Medical Center (USA)	5	418
Cantinotti M	Fondazione Toscana G. Monasterio (Italy)	5	119
Clerico A	1. Fondazione Toscana G. Monasterio (Italy) 2. Scuola Superiore Sant'Anna (Italy)	5	119
Hobbs CA	University of Arkansas for Medical Sciences (USA)	4	184
James SJ	University of Arkansas for Medical Sciences (USA)	4	184
Murzi B	Fondazione Toscana G. Monasterio (Italy)	4	101
Zhao WZ	University of Arkansas for Medical Sciences (USA)	3	166
Fineman JR	University of California (USA)	3	95
Han SP	Nanjing Medical University (China)	3	92
Yu ZB	Nanjing Medical University (China)	3	92
Crocetti M	Fondazione Toscana G. Monasterio (Italy)	3	81
Cleves MA	University of Arkansas for Medical Sciences (USA)	3	76
Bauersachs J	Hannover Medical School (Germany)	3	70
Tutarel O	Hannover Medical School (Germany)	3	70
Westhoff-Bleck M	Hannover Medical School (Germany)	3	70
Storti S	Fondazione Toscana G. Monasterio (Italy)	3	54

Table 4 The institutions contributed three or more to top 100 cited articles on biomarkers in congenital heart disease

Institution	N	Total citations
University of Cincinnati College of Medicine (USA)	5	399
Fondazione Toscana G. Monasterio (Italy)	5	227
University of Arkansas for Medical Sciences (USA)	4	184
Scuola Superiore Sant'Anna (Italy)	4	178
Erasmus University Medical Center (The Netherlands)	4	118
Hannover Medical School (Germany)	4	108
Cincinnati Children's Hospital (USA)	4	102
CNR Institute of Clinical Physiology (Italy)	3	241
University of California (USA)	3	95
Nanjing Medical University (China)	3	92
Yale University (USA)	3	77

curves represent paths of references, originating from the citing map on the left and pointing to the cited map on the right (31). There were two main citation paths (both green) shown on the map. The green paths mean papers published in medicine/medical/clinical mostly cited journals in molecular/biology/genetics, health/nursing/medicine. *Figure 6* showed the most frequently cited journals (occurrences ≥20) in the co-citation analysis.

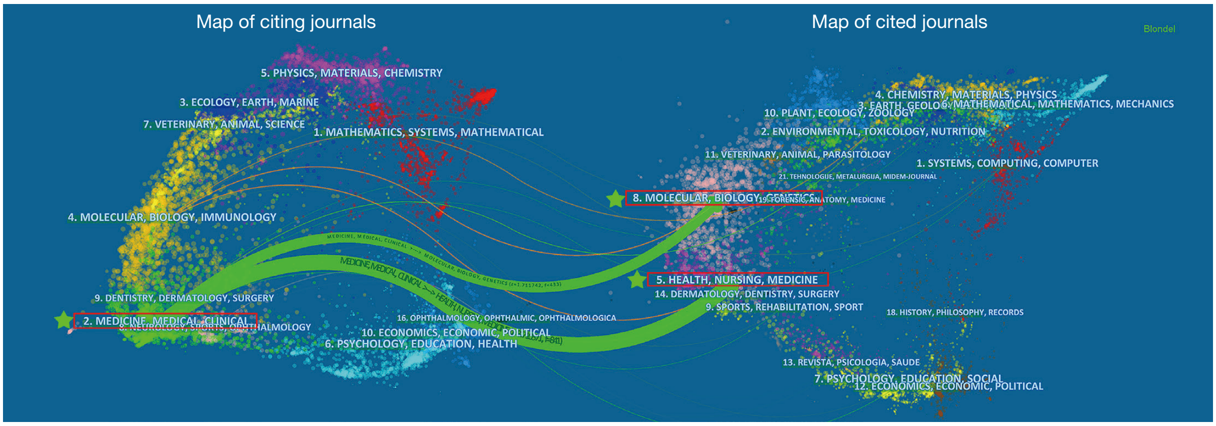

Figure 5 The dual-map overlay of journals related to biomarkers in congenital heart disease. Produced by CiteSpace 5.7.R3 (Drexel University, Philadelphia, PA, USA). The green paths are the main citation paths: Papers published in medicine/medical/clinical mostly cited journals in molecular/biology/genetics, health/nursing/medicine.

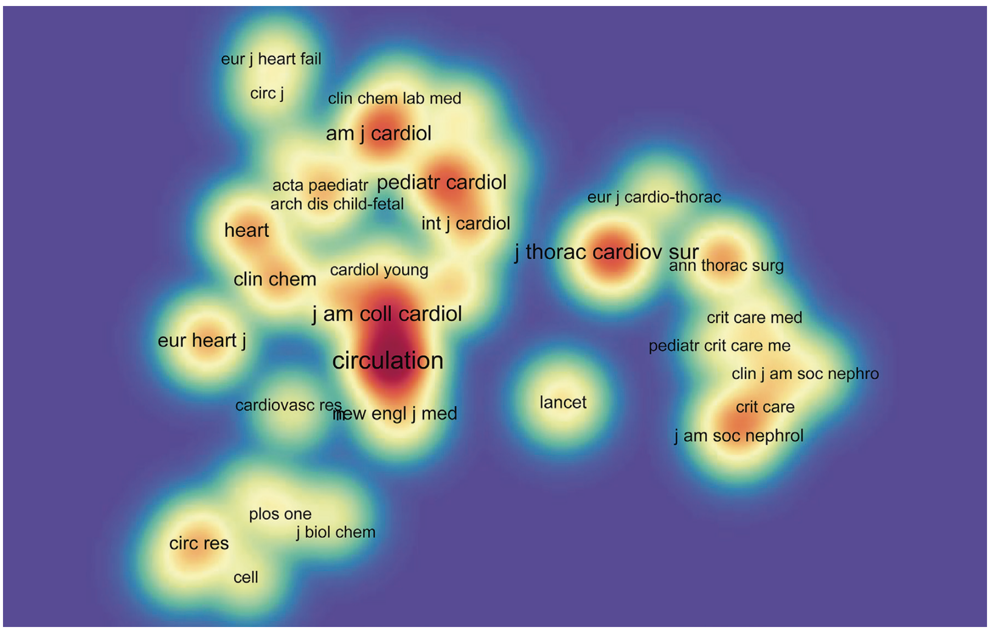

Figure 6 Hotspot of the source of the journal with co-citation references. Produced by VOSviewer 1.6.9 (Leiden University, Leiden, The Netherlands).

Keywords mapping

A total of 626 keywords were extracted and the total frequency of occurrence was 1,209. In *Table 5*, the 18 keywords with eight or more times presented were listed. In CiteSpace, we set the same parameters as the co-cited references citation bursts analysis, and no keyword bursts were detected during the period from 2001 to 2017. Clustering analysis for keywords occurred five or more times was presented in *Figure 7*, which divided into four clusters. The keywords with high frequency can accurately reveal the main topic of a field. *Table 6* shows the four clusters describing disease conditions (such as heart failure) and surrogate parameters (such as proBNP) in the keyword cluster analysis. The terms "congenital heart disease" and "biomarkers" were the subject in this bibliometric analysis and were not included in any cluster.

Table 5 The high frequency keywords on biomarkers in congenital heart disease (occurrences ≥8)

Rank	Keyword	Occurrences
1	Congenital heart disease	39
1	Biomarkers	39
3	Children	28
4	Cardiac-surgery	16
5	Brain natriuretic peptide	14
5	Cardiopulmonary bypass	14
5	Infants	14
5	Risk	14
9	Acute renal failure	11
9	Dysfunction	11
9	Failure	11
12	Congenital heart defect	10
12	Natriuretic peptides	10
14	Acute kidney injury	9
14	Expression	9
14	Heart failure	9
17	Mortality	8
17	Patent ductus-arteriosus	8

Discussion

In 1987, Garfield published the first analysis of top-cited articles in *JAMA* (32). Similar citation analysis had subsequently been performed in many fields of medicine to provide useful information on aspects such as the types and levels of evidence in the articles, the most frequently studied topics, the historical development of the field, and current research trends (33,34). The total number of citations that a published article has achieved indicates the importance that the published article has on that area of practice. Analysis of the most influential publications can be helpful in recognizing main and novel issues within a specific field.

This study conducted the first bibliometric review of publications, contributions, authors, countries, and institutions related to biomarkers in CHD, and identified the most commonly cited publications and journals. The analysis not only to provide recognition to the most prolific entities in the field, but also helps agencies guide their limited resources toward authors and institutions that continuously produce high-quality work. Furthermore, this information can help researchers find potential collaborators in the field.

From 1996 to 2017, the most published literature was included in 21 years, and the absence of literature in the recent three years also indicated that recently published papers need a period of exposure time to increase their citation, which requires at least three years. Numerous factors contribute to total citations, of which the older the article was dated the more citations it tended to accumulate. This effect of time can be further explained by scientific articles reaching their peak number of citations three to ten years after publication, after which they were cited at a less recurring rate.

We explored whether the IF of a journal affects the number of citations of a paper. Journals with high IF usually attract high-quality papers, and the excellent papers can further enhance the academic influence in turn, which forms a positive feedback effect. In our analysis, journals with high IF deviated from the range confirmed this theory (35). While the journals in the upper left corner of *Figure 2* were authoritative journals in this field (18,36-39), this indicated that high-quality articles in a specific field were more willing to be published in professional related journals rather than some comprehensive journals with higher IF. The outlier journals with high IF below the fitting range in the *Figure 2* showed an inconsistent citation frequency. To analyze the reason for this phenomenon, some papers published in these journals were in recent years (40), and elapsed time was needed for these articles to spread and accumulate citations. There are also some articles published in comprehensive journals, which may affect the citation frequency of articles (41).

The geographic distribution of the network map of biomarkers in CHD field showed that the USA was the most productive country in terms of total publications and total citations. Most of the top 11 institutions were from the USA. This finding is consistent with previous findings that cardiovascular research activities are directly correlated with the human development index and negatively correlated with CVD burden (42). The possible reasons for developing countries with a low output may be inadequate funding, political instability, and a lack of enthusiasm and inclination for research in this area. There was no significant trend in cooperation between institutions, and it suggested that cross-institutional cooperation should be carried out to jointly improve its scientific research capabilities.

From the type of literature included, we found that the

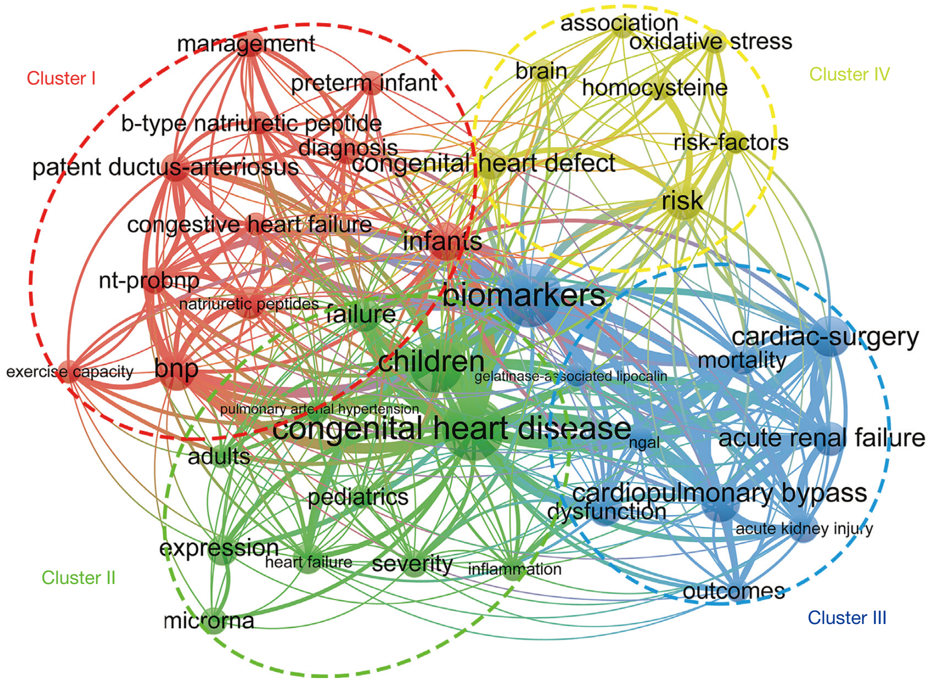

Figure 7 The network map of keywords for the top 100 most cited articles on biomarkers in congenital heart disease. Produced by VOSviewer 1.6.9 (Leiden University, Leiden, The Netherlands).

Table 6 Disease conditions and surrogate parameters in the keyword cluster analysis

Cluster	Conditions	Surrogate parameters
Cluster I	Patent ductus-arteriosus, congestive heart failure, exercise capacity, preterm infant, infants, diagnosis, management	Brain natriuretic peptide, natriuretic peptides, NT-proBNP, b-type natriuretic peptide
Cluster II	Children, pediatrics, adults, pulmonary arterial hypertension, failure, heart failure, expression, severity	Inflammation, microRNA
Cluster III	Cardiac-surgery, cardiopulmonary bypass, acute renal failure, acute kidney injury, dysfunction, outcomes, mortality	Gelatinase-associated lipocalin, NGAL
Cluster IV	Congenital heart defect, brain, risk-factors, risk, association	Homocysteine, oxidative stress

original research accounted for the majority, while the review articles were few, which indicates that this field was in its infancy and more research was needed to promote more review articles. Collaboration between authors was mainly concentrated in the same research group in the same institution while 90.20% of authors only published one top-100 article, indicating the authors continued to participate in high-cited articles on biomarkers in CHD field was few.

Our findings support the application of Bradford's law, a bibliometric concept suggested by Brookes (43,44). The principle idea behind Bradford's law was that most researchers obtained their citations from a few main journals in their respective field of expertise. When the researchers deviate from these core journals, their citation frequency and impact were weakened. Consequently, this tendency led to a large percentage of citations stemming from a few core journals. In summary, we identified and analyzed the co-citation characteristics of the 100 most-cited articles of biomarkers in CHD, and some core journals in this field were identified. The characteristics of these journals, highly cited references can show that prolific leading position in this field.

Four clusters were obtained after cluster analysis, which represents the four research hotspots in this field. Cluster I was the application of natriuretic peptide in CHD. The natriuretic peptide is a common and reliable biomarker in CVD. Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) can be used for comprehensive evaluation and monitoring of children with CHD, to further determine the severity and progress of heart failure and its response to treatment. BNP/NT-proBNP can also be used as an auxiliary marker for screening CHD with hemodynamic significance and prognosis of children undergoing cardiac surgery (45,46). Cluster II indicated that some genes and their related transcriptional translation agents as biomarkers were associated with prognosis or predicted the occurrence of CHD. There is a growing interest to use circulating biomarkers for risk stratification in patients with CHD such as bicuspid aortic valve. The following biomarkers are being focused on: matrix metalloproteinases (MMPs), transforming growth factor β (TGF-β), tissue inhibitors of matrix metalloproteinases (TIMPs), alpha1-antitrypsin, as well as non-coding microRNAs (47,48). Cluster III represented biomarkers in secondary injury after cardiopulmonary bypass in children with CHD, such as Neutrophil gelatinase-associated lipocalin (NGAL) and SB100 protein, which mainly involved the prediction and evaluation of kidney injury and brain injury after extracorporeal circulation (49,50). The concentration of NGAL in urine and serum represents a sensitive, specific and highly predictive early biomarker of acute kidney injury after cardiac surgery. After cardiac surgery with cardiopulmonary bypass, the brain oxygenation of infants with increased S100B concentrations is impaired during perioperative period. Astrocyte protein S100B can be used as an alternative parameter for cerebral hypoxemia after surgery for CHD. Cluster IV represented the application of biomarkers such as homocysteine, NO, and oxidative stress in the assessment of general state and cardiac injury in CHD. Identifying the nature and extent of alterations in biomarkers such as homocysteine, NO, and oxidative stress, may suggest primary intervention strategies and provide clues to a greater understanding of the pathogenesis of CHD (51,52). Keywords cluster analysis pointed out that research in these fields will still be the focus in the next few years. This may serve as a guide for the use of limited medical funding resources and for the selection of topics for young researchers.

Limitations

There were some limitations in our analysis. (I) According to the time distribution of the included literature, the application of biomarkers in CHD was relatively new. Only 60 of the top 100 literature had been cited more than 20 times, indicating that this field had not received extensive attention in the past. The quantitative bibliometric analysis needed more high impact articles in this field to reflect the general characteristics. At this time, our main aim of this analysis was summarized the future research trends, so that the limited research funding input can get effective output. Five years or ten years later, an updated quantitative analysis in this field may have a renewal in the list of top-100 article, but the overall basic characteristics and research direction reflected should not change greatly. (II) We chosen WoS core database instead of Scopus as our retrieval source database. While focusing on the quality of journal sources, we relatively missed some journals that were not included in JCR. (III) We have performed manual standardization for some keywords. This process aims to reduce the bias caused by different expressions of the same phrase, but the influence of the bias on the analysis cannot be completely eliminated.

Conclusions

According to this bibliometric study, research of biomarkers in CHD field had increased interest in these years and we also highlighted the global research trends, research subjects, and collaboration network between countries. The future research hotspots in this field were listed as follows: (I) the application of natriuretic peptide, (II) the diagnostic and prognostic value of genes and their related transcriptional translation agents, (III) the use of biomarkers to evaluate and predict the postoperative injury caused by extracorporeal circulation, (IV) and the application of other biomarkers (such as oxidative stress, homocysteine, and thrombosis) to assess and predict damage circumstance. The findings provided insight for policy-makers and researchers in making decisions, agreeing with future research precedence and contributing to continuing development in this dynamic field.

Acknowledgments

Funding: This study was supported by the Gansu Province

Science and Technology Plan Funded Project under project number 20CX4ZA027 & 20CX9ZA112, Natural Science Foundation of Gansu Province under project number 21JR1RA027, and Health industry scientific research project of Gansu Province under project number GSWSKY2016-04.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2422/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:2241-7.
2. Liu Y, Chen S, Zühlke L, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol 2019;48:455-63.
3. Muntean I, Togănel R, Benedek T. Genetics of Congenital Heart Disease: Past and Present. Biochem Genet 2017;55:105-23.
4. Blue GM, Kirk EP, Sholler GF, et al. Congenital heart disease: current knowledge about causes and inheritance. Med J Aust 2012;197:155-9.
5. Zaidi S, Brueckner M. Genetics and genomics of congenital heart disease. Circ Res 2017;120:923-40.
6. Khairy P, Ionescu-Ittu R, Mackie AS, et al. Changing mortality in congenital heart disease. J Am Coll Cardiol 2010;56:1149-57.
7. Kempny A, Dimopoulos K, Uebing A, et al. Outcome of cardiac surgery in patients with congenital heart disease in England between 1997 and 2015. PLoS One 2017;12:e0178963.
8. GBD 2017 Congenital Heart Disease Collaborators. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Child Adolesc Health 2020;4:185-200.
9. Bouma BJ, Mulder BJ. Changing Landscape of Congenital Heart Disease. Circ Res 2017;120:908-22.
10. Triedman JK, Newburger JW. Trends in Congenital Heart Disease: The Next Decade. Circulation 2016;133:2716-33.
11. Vijlbrief DC, Benders MJ, Kemperman H, et al. Use of cardiac biomarkers in neonatology. Pediatr Res 2012;72:337-43.
12. Dobson R, Walker HA, Walker NL. Biomarkers in congenital heart disease. Biomark Med 2014;8:965-75.
13. Hauser JA, Demyanets S, Rusai K, et al. Diagnostic performance and reference values of novel biomarkers of paediatric heart failure. Heart 2016;102:1633-9.
14. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation 2006;113:2335-62.
15. Magnussen C, Blankenberg S. Biomarkers for heart failure: small molecules with high clinical relevance. J Intern Med 2018;283:530-43.
16. McCarthy CP, McEvoy JW, Januzzi JL Jr. Biomarkers in stable coronary artery disease. Am Heart J 2018;196:82-96.
17. Dhingra R, Vasan RS. Biomarkers in cardiovascular disease: Statistical assessment and section on key novel heart failure biomarkers. Trends Cardiovasc Med 2017;27:123-33.
18. Baumgartner H, De Backer J, Babu-Narayan SV, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J 2021;42:563-645.
19. Barragán Martín AB, Molero Jurado MDM, Pérez-Fuentes MDC, et al. Study of Cyberbullying among Adolescents in Recent Years: A Bibliometric Analysis. Int J Environ Res Public Health 2021;18:3016.
20. Chen Y, Cheng L, Lian R, et al. COVID-19 vaccine research focusses on safety, efficacy, immunoinformatics, and vaccine production and delivery: a bibliometric analysis based on VOSviewer. Biosci Trends 2021;15:64-73.
21. Gao Y, Shi S, Ma W, et al. Bibliometric analysis of global

research on PD-1 and PD-L1 in the field of cancer. Int Immunopharmacol 2019;72:374-84.
22. Li F, Li M, Guan P, et al. Mapping publication trends and identifying hot spots of research on Internet health information seeking behavior: a quantitative and co-word biclustering analysis. J Med Internet Res 2015;17:e81.
23. You Y, Min L, Tang M, et al. Bibliometric Evaluation of Global Tai Chi Research from 1980-2020. Int J Environ Res Public Health 2021;18:6150.
24. Waltman L, van Eck NJ, Noyons ECM. A unified approach to mapping and clustering of bibliometric networks. J Informetr 2010;4:629-35.
25. Gao Y, Ge L, Shi S, et al. Global trends and future prospects of e-waste research: a bibliometric analysis. Environ Sci Pollut Res Int 2019;26:17809-20.
26. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. Proc Natl Acad Sci U S A 2004;101 Suppl 1:5303-10.
27. Liu M, Gao Y, Yuan Y, et al. Global hotspots and future prospects of chimeric antigen receptor T-cell therapy in cancer research: a bibliometric analysis. Future Oncol 2020;16:597-612.
28. Egghe L, Rao IKR. Study of different h-indices for groups of authors. J Am Soc Inf Sci Techno 2008;59:1276-81.
29. Taggart DP, Hadjinikolas L, Wong K, et al. Vulnerability of paediatric myocardium to cardiac surgery. Heart 1996;76:214-7.
30. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365:1231-8.
31. Chen C, Leydesdorff L. Patterns of connections and movements in dual-map overlays: A new method of publication portfolio analysis. J Am Soc Inf Sci Technol 2014;65:334-51.
32. Garfield E. 100 citation classics from the Journal of the American Medical Association. JAMA 1987;257:52-9.
33. Shi S, Gao Y, Liu M, et al. Top 100 most-cited articles on exosomes in the field of cancer: a bibliometric analysis and evidence mapping. Clin Exp Med 2021;21:181-94.
34. Usman MS, Siddiqi TJ, Khan MS, et al. A Scientific Analysis of the 100 Citation Classics of Valvular Heart Disease. Am J Cardiol 2017;120:1440-9.
35. Andreassi MG, Ait-Ali L, Botto N, et al. Cardiac catheterization and long-term chromosomal damage in children with congenital heart disease. Eur Heart J 2006;27:2703-8.
36. Hirsch R, Dent C, Pfriem H, et al. NGAL is an early predictive biomarker of contrast-induced nephropathy in children. Pediatr Nephrol 2007;22:2089-95.
37. Hobbs CA, Cleves MA, Melnyk S, et al. Congenital heart defects and abnormal maternal biomarkers of methionine and homocysteine metabolism. Am J Clin Nutr 2005;81:147-53.
38. Ait-Ali L, Andreassi MG, Foffa I, et al. Cumulative patient effective dose and acute radiation-induced chromosomal DNA damage in children with congenital heart disease. Heart 2010;96:269-74.
39. Mayr M, Zhang J, Greene AS, et al. Proteomics-based development of biomarkers in cardiovascular disease: mechanistic, clinical, and therapeutic insights. Mol Cell Proteomics 2006;5:1853-64.
40. Forte A, Bancone C, Cobellis G, et al. A Possible Early Biomarker for Bicuspid Aortopathy: Circulating Transforming Growth Factor β-1 to Soluble Endoglin Ratio. Circ Res 2017;120:1800-11.
41. Todd Tzanetos DR, Yu C, Hernanz-Schulman M, et al. Prospective study of the incidence and predictors of thrombus in children undergoing palliative surgery for single ventricle physiology. Intensive Care Med 2012;38:105-12.
42. Ellul T, Bullock N, Abdelrahman T, et al. The 100 most cited manuscripts in emergency abdominal surgery: A bibliometric analysis. Int J Surg 2017;37:29-35.
43. Garfield E. Bradford law and related statistical patterns. Current Contents 1980;19:5-12.
44. Venable GT, Shepherd BA, Loftis CM, et al. Bradford's law: identification of the core journals for neurosurgery and its subspecialties. J Neurosurg 2016;124:569-79.
45. Cantinotti M, Law Y, Vittorini S, et al. The potential and limitations of plasma BNP measurement in the diagnosis, prognosis, and management of children with heart failure due to congenital cardiac disease: an update. Heart Fail Rev 2014;19:727-42.
46. Giannakoulas G, Dimopoulos K, Bolger AP, et al. Usefulness of natriuretic Peptide levels to predict mortality in adults with congenital heart disease. Am J Cardiol 2010;105:869-73.
47. Girdauskas E, Neumann N, Petersen J, et al. Expression Patterns of Circulating MicroRNAs in the Risk Stratification of Bicuspid Aortopathy. J Clin Med 2020;9:276.
48. Obermann-Borst SA, van Driel LM, Helbing WA, et al. Congenital heart defects and biomarkers of methylation in children: a case-control study. Eur J Clin Invest 2011;41:143-50.
49. Hansen JH, Kissner L, Logoteta J, et al. S100B and its

relation to cerebral oxygenation in neonates and infants undergoing surgery for congenital heart disease. Congenit Heart Dis 2019;14:427-37.
50. Nishida M, Kubo S, Morishita Y, et al. Kidney injury biomarkers after cardiac angiography in children with congenital heart disease. Congenit Heart Dis 2019;14:1087-93.
51. Caputo M, Mokhtari A, Miceli A, et al. Controlled reoxygenation during cardiopulmonary bypass decreases markers of organ damage, inflammation, and oxidative stress in single-ventricle patients undergoing pediatric heart surgery. J Thorac Cardiovasc Surg 2014;148:792-801.e8; discussion 800-1.
52. Hobbs CA, Cleves MA, Zhao W, et al. Congenital heart defects and maternal biomarkers of oxidative stress. Am J Clin Nutr 2005;82:598-604.

Cite this article as: Yi K, Xu JG, Yang KL, Zhang X, Ma L, You T, Tian JH. The top-100 most cited articles of biomarkers in congenital heart disease: a bibliometric analysis. Ann Palliat Med 2022;11(5):1700-1713. doi: 10.21037/apm-21-2422

Supplementary

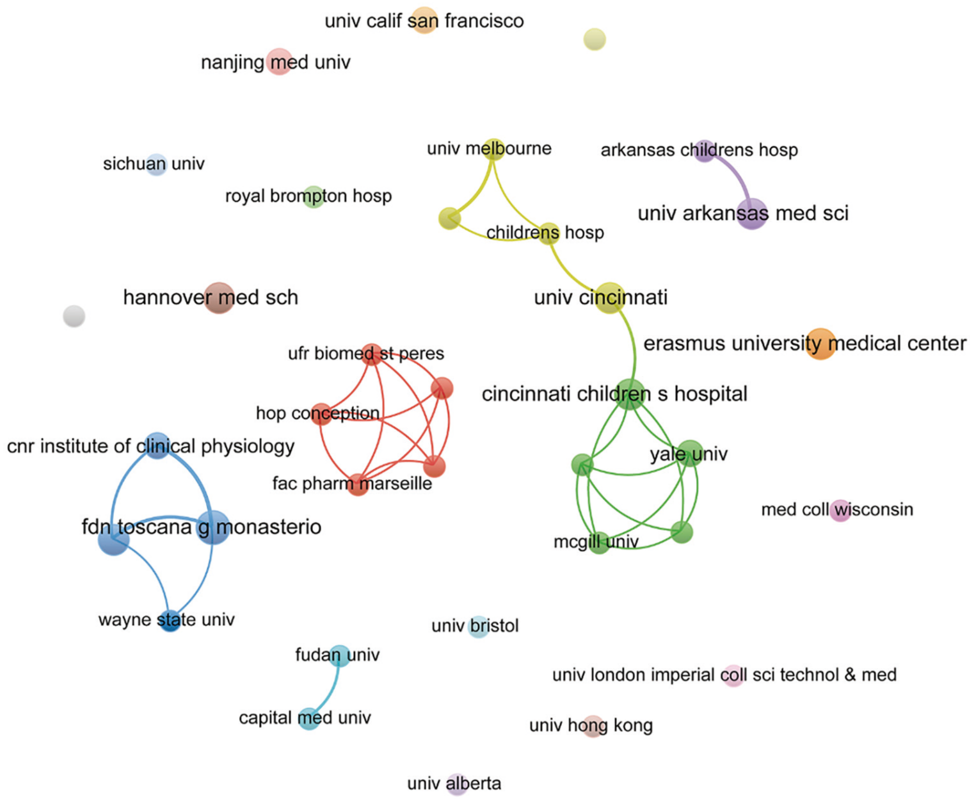

Figure S1 The network map of institutions for the biomarkers in congenital heart disease. Produced by VOSviewer 1.6.9 (Leiden University, Leiden, The Netherlands)

https://dx.doi.org/10.21037/apm-21-2422

Table S1 Journals contributed to the 100 top-cited articles

Rank	Journal	N	Cited Number	Country	IF
1	Pediatric Cardiology	8	190	USA	1.564
2	Journal of Thoracic and Cardiovascular Surgery	5	161	USA	4.451
3	International Journal of Cardiology	5	125	Ireland	3.229
4	Plos One	4	125	USA	2.74
5	American Journal of Cardiology	4	171	USA	2.57
6	Circulation	3	256	USA	23.603
7	Heart	3	191	UK	5.213
8	Clinical Chemistry and Laboratory Medicine	3	89	Germany	3.595
9	Pediatric Nephrology	3	363	USA	2.676
10	Circulation Journal	3	84	Japan	2.54
11	Intensive Care Medicine	2	46	USA	17.679
12	American Journal of Clinical Nutrition	2	146	USA	6.766
13	Critical Care	2	100	UK	6.407
14	Annals of Thoracic Surgery	2	84	USA	3.639
15	European Journal of Cardio-Thoracic Surgery	2	40	Netherlands	3.486
16	Reproductive Toxicology	2	46	USA	3.121
17	Pediatric Critical Care Medicine	2	87	USA	2.854
18	Neonatology	2	38	Switzerland	2.742
19	Clinica Chimica Acta	2	64	Netherlands	2.615
20	Birth Defects Research Part A-Clinical and Molecular Teratology	2	38	USA	2.146
21	Acta Paediatrica	2	30	Denmark	2.111
22	Congenital Heart Disease	2	41	USA	1.663
23	Heart and Vessels	2	43	Japan	1.618
24	European Heart Journal	1	95	UK	22.673
25	Circulation Research	1	15	USA	14.467
26	European Journal of Heart Failure	1	15	Netherlands	11.627
27	Chest	1	38	USA	8.308
28	Critical Care Medicine	1	19	USA	7.414
29	Clinical Journal of The American Society of Nephrology	1	38	USA	6.628
30	American Journal of Obstetrics and Gynecology	1	24	USA	6.502
31	Cellular Physiology and Biochemistry	1	24	Switzerland	5.5
32	Archives of Disease in Childhood-Fetal and Neonatal Edition	1	39	USA	5.436
33	Pediatrics	1	18	USA	5.359
34	Molecular & Cellular Proteomics	1	62	USA	4.87
35	Bjog-An International Journal of Obstetrics and Gynaecology	1	28	UK	4.663
36	Anesthesia and Analgesia	1	23	USA	4.305
37	Journal of Translational Medicine	1	24	UK	4.124
38	Journal of Pediatrics	1	77	USA	3.7
39	Heart Failure Reviews	1	48	Netherlands	3.538
40	European Journal of Clinical Investigation	1	30	Germany	3.481
41	Seminars in Perinatology	1	25	USA	3.231
42	Cytokine	1	30	UK	2.952
43	Neurocritical Care	1	15	USA	2.72
44	Clinical Biochemistry	1	23	Canada	2.573
45	Pediatric Anesthesia	1	21	UK	2.311
46	Journal of Cardiothoracic and Vascular Anesthesia	1	20	USA	2.258
47	Current Opinion in Pediatrics	1	24	USA	2.114
48	Bmc Cardiovascular Disorders	1	20	UK	2.078
49	Swiss Medical Weekly	1	25	Switzerland	1.822
50	Bmc Medical Imaging	1	22	UK	1.792
51	Experimental and Therapeutic Medicine	1	26	Greece	1.785
52	Clinical and Experimental Nephrology	1	39	Japan	1.77
53	Medical Hypotheses	1	22	UK	1.375
54	Indian Pediatrics	1	15	India	1.186
55	Pediatrics International	1	17	Japan	1.139
56	Cardiology in The Young	1	17	USA	1

Note: IF: Impact factor (InCites Journal Citation Reports dataset updated Jun 29, 2020).

https://dx.doi.org/10.21037/apm-21-2422