Frontiers and Emerging Trends in Cardiorenal Syndrome biomarker: A Bibliometric and Visualized Analysis from 2003 to 2022

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Abstract

**Background:** Since the term of Cardiorenal syndrome (CRS) was proposed, the field has attracted much attention, and research on biomarkers of CRS has gradually emerged. Now, many CRS biomarkers have been identified and applied in clinical practice for disease diagnosis, treatment guidance, prognosis prediction and so on. In this study, bibliometrics was used to analyze the current status, research hotspots and frontiers of CRS biomarkers, in order to provide some valuable information for the research in this field.

**Methods:** Literature related to CRS biomarkers in the Web of Science database from 2003 to 2022 was searched. Based on CiteSpace, Vosviewer software and R program, the bibliometrics method was adopted to conduct quantitative retrospective analysis, visual presentation and result interpretation of the included literatures.

**Results:** A total of 577 literatures related to CRS biomarkers were included. Since the study was carried out, the number of published papers has been on the rise. The United States dominates the field; The San Bortolo Hosp's publication ranks first; Claudio Ronco is the most influential author in the field, with an absolute advantage in the number of publications and citations. CARDIORENAL MEDICINE (IF=4.36) is the most published journal focusing on CRS research. Finally, the biomarkers and research hotspots of CRS are introduced.

**Conclusion:** The exploration of new biomarkers is still a hotspot in this field, and their value in efficacy and prognosis is a potential research direction. Exploring the mechanism of disease and pathophysiology may be the forefront of research in this field in the future.

1 Introduction

The heart and kidney play an essential role in the human body and are closely linked in pathophysiology. "Organ crosstalk" refers to the complex physiological communication between different systems of the body, which is necessary for optimal balance and function of the organism. Crosstalk between the kidney and heart was first described by Bright1 in 1836 by exploring the pathological links and causal relationships between cardiovascular risk and kidney disease, since then, the exploration direction of heart and kidney research has been opened up. Cardiorenal syndrome (CRS) was first proposed by Ledoux2 in 1951. In 2004, the NHLBI Working Group described CRS as a disease state in which treatment to improve the symptoms of heart failure (HF) is limited by further deterioration of renal function. However, some scholars believe that this description does not adequately reflect the complexity and bidirectional nature of the pathophysiological interactions between the heart and kidney.3 In 2005, Bongartz et al. proposed and emphasized that CRS is a very serious complex disease in which the pathophysiology of both interact, failure of the heart function exacerbates renal dysfunction and renal failure promotes the development of cardiac dysfunction4. In 2008, Claudio Ronco et al. defined CRS as an acute or chronic lesion of one organ (heart or kidneys) caused by an acute or chronic lesion of another organ. And CRS
typing was first proposed as well as described, they classified CRS into five types. In 2010, the report of the Acute Dialysis Quality Initiative (ADQI) Consensus Conference in 2010 clarified the concept of CRS as a clinical syndrome caused by acute or chronic injury to another organ due to acute or chronic insufficiency of either the heart or kidney and also clarified the five CRS subtypes and definitions, which are used to this day. There is no epidemiological evidence directly addressing the prevalence of CRS, but one study showed that the prevalence of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) aged 66 years or older was 64.5%, almost twice as high as in patients without CKD (prevalence of 32.4%). When heart and kidney disease occur together, they lead to higher mortality and readmission rates and worse prognoses. Antonietta Gigante et al. found through a clinical retrospective cohort study that type 1 CRS was the most morbid and mortal category in their study. During the treatment of CRS, the use of diuretics is the main method to reduce volume overload, while diuretic resistance often occurs in the end stages of CRS, which undoubtedly increases the difficulty of treatment again, so early diagnosis and treatment of CRS are clinically significant. Biomarkers are indicators of physiological states, pathological processes, as well as collective responses following drug utilization, and are widely used in the clinic for diagnosis, efficacy assessment, and prognosis prediction. Robert M Califf et al. classified biomarkers into diagnostic, efficacy, prognostic, predictive, safety, and monitoring categories based on their functions, and the same marker can have multiple functional attributes. Biomarkers can identify the early appearance of cardiac and/or renal injury and play a key role in reducing the morbidity and mortality of CRS, thereby improving prognosis through timely and effective treatment.

Biomarkers are one of the hot research topics within the field of CRS. Due to the specificity of CRS, biomarkers are mostly divided into cardiac or renal biomarkers, and novel markers are still emerging. Therefore, it is necessary to systematically review and summarize the hotspots in the development and plan future research directions.

Bibliometrics analysis refers to the analysis of publications, authors, and vocabulary in a quantitative way, using mathematical and statistical methods. It provides a model for quantitatively analyzing scientific publications to capture the hotspots, knowledge structure, and future emerging trends in the research field. Lv et al. analyzed the publications related to CRS in the Web of Science Core Collection (WoSCC) database from 2003 to 2022, focusing on advances and trends in CRS pathophysiology, diagnostic pathways, and treatment strategies. However, there have been no reported studies targeting the bibliometrics analysis of CRS biomarkers. Therefore, we conducted this study to perform a metrological analysis of the publications related to CRS biomarkers using software such as CiteSpace and Vosviewer to explore research hotspots and research trends in this field.

2 Materials And Methods

2.1 Data Sources and Retrieval Strategies
Web of Science (WoS) is a database covering multidisciplinary publications with great influence and authority worldwide. Due to the small number of publications retrieved from PubMed and a large amount of duplication with WoS, we decided to conduct a literature retrieval in the Web of Science Core Collection (WoSCC) database to ensure data quality and integrity. The publication time was from January 1, 2003, to October 20, 2022. The search strategy was: ((((TS=(biomarkers )) OR TS=(markers)) OR TS=(diagnosis)) OR TS=(prognosis)) AND TS=(cardiorenal syndrome). The language of publication was limited to English. The search was conducted by the investigator (MXX) on October 21, 2022, and the publications were exported on the same day to ensure accuracy. Two researchers (MXX, FZY) independently screened the publications and checked each other. And if there was any ambiguity, a third researcher (SQQ) assisted in decision-making. A total of 603 documents were retrieved and screened, and 577 documents were finally included, including 433 articles and 144 reviews.

2.2 Data Extraction and Analysis

The incorporated publications were imported into Citespace and VOSviewer software to extract information on publications, countries/regions, institutions, source journals, authors, keywords, references, etc., and visualized for analysis. Regarding the parameter function selection, the time was chosen from 2003 to 2022 with a time slice of 1 year; using the pathfinding pruning method and the minimum spanning tree algorithm, top = 50 was selected as the threshold value and other values were set as the default values in Citespace. The 2022 impact factor (IF) was used to reflect the quality or influence of journals/literature, and the H-index was used to evaluate the output power or academic status of countries, institutions as well as journals. In the visualization mapping of this paper, nodes represent countries, institutions, authors, keywords, and references; the size of nodes is positively correlated with the number or frequency; the color of nodes indicates clusters, and the same clusters are grouped and presented in the same color; the connecting lines between nodes represent associations, and the thickness of the lines reflects the strength of the connecting associations. The trendline figure of publication volume and the timeline figure are used to show the dynamic evolution of each element at a certain time or stage. The burst analysis graph represents the hot research trends at a certain time or stage to show the hot evolution of the field.

3 Results Of Visualization

3.1 Annual publications

Between January 1, 2003, and October 20, 2022, 577 CRS biomarker-related articles were published in WoS. There has been an overall cumulative upward trend since 2003. Figure 1A illustrates the number of publications per year. The first retrieved study related to CRS biomarkers was published in 2003, the number of publications grew slowly between 2003–2009 and began to show rapid growth after 2009, reaching a peak in 2015. Notably, as of October 20, 2022, 56 relevant papers have been published in the current year, accounting for 9.53% of the total. The trendline \[Y = 2.8714X \ (R^2 = 0.8573)\] was fitted to the
annual volume data to predict the future volume size. (Fig. 1B) Articles accounted for 75.04% and Reviews for 24.96% of the included publications. (Fig. 1C)

### 3.2 Distribution characteristics of countries or regions

Between 2003 and 2022, 55 countries and regions published studies related to biomarkers of the CRS, and their distribution characteristics are shown in Fig. 2A. Among the top 10 contributing countries, the highest number of publications was from the United States (n = 184), followed by Italy (n = 96) and China (n = 66) (Fig. 2B). The highest number of citations was in the United States (n = 7207), followed by Italy (n = 5087) and Canada (n = 3509) (Fig. 2C). The highest H-index was in the United States (n = 86), followed by Canada (n = 46) and Italy (n 40) (Fig. 2D).

### 3.3 Distribution characteristics of institutions

In the last two decades, 1113 institutions have conducted and published studies associated with biomarkers of CRS. The top 10 contributing institutions published 159 articles, accounting for 27.56% of the total (Table 1). Among them, San Bortolo Hosp published the maximum number of articles (n = 28), followed by Univ Groningen (n = 20) and Chang Gung Univ (n = 16). The most cited institution remained San Bortolo Hosp (n = 1730). We used Citespace to analyze the collaboration network among institutions (Fig. 3A) and the trend of annual publication volume of the top 10 institutions (Fig. 3B). As seen in Fig. 3A, the network nodes of San Bortolo Hosp, Univ Groningen, and Duke Univ are not only located at the center of the collaborative network but are also more closely connected to other institutions.
Table 1
Top 10 productive institutions in CRS biomarkers from 2003 to 2022

<table>
<thead>
<tr>
<th>Rank</th>
<th>Institutions</th>
<th>Article counts</th>
<th>Proportion</th>
<th>Total number of Citations</th>
<th>Average number of citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>San Bortolo Hosp</td>
<td>28</td>
<td>4.85</td>
<td>1730</td>
<td>61.7857</td>
</tr>
<tr>
<td>2</td>
<td>Univ Groningen</td>
<td>20</td>
<td>3.47</td>
<td>1212</td>
<td>60.6</td>
</tr>
<tr>
<td>3</td>
<td>Chang Gung Univ</td>
<td>16</td>
<td>2.77</td>
<td>254</td>
<td>15.875</td>
</tr>
<tr>
<td>4</td>
<td>Duke Univ</td>
<td>15</td>
<td>2.60</td>
<td>680</td>
<td>45.3333</td>
</tr>
<tr>
<td>5</td>
<td>Univ Alberta</td>
<td>15</td>
<td>2.60</td>
<td>701</td>
<td>46.7333</td>
</tr>
<tr>
<td>6</td>
<td>Yale Univ</td>
<td>15</td>
<td>2.60</td>
<td>925</td>
<td>61.6667</td>
</tr>
<tr>
<td>7</td>
<td>Univ Padua</td>
<td>14</td>
<td>2.43</td>
<td>980</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>Cleveland Clin</td>
<td>13</td>
<td>2.25</td>
<td>671</td>
<td>51.6154</td>
</tr>
<tr>
<td>9</td>
<td>Baylor Univ</td>
<td>12</td>
<td>2.08</td>
<td>727</td>
<td>60.5833</td>
</tr>
<tr>
<td>10</td>
<td>Univ Brescia</td>
<td>11</td>
<td>1.91</td>
<td>427</td>
<td>38.8182</td>
</tr>
</tbody>
</table>

3.4 Journal analysis

A total of 255 journals have published articles on biomarkers of CRS since 2003. We enumerated the top 10 journals that made the greatest contributions (Table 2) and found that they published 120 articles, accounting for 20.80% of the total. CARDIORENAL MEDICINE was the most productive journal (n = 27). Visual analysis using R software to obtain the Sankey figure linking authors, keywords, and literature sources revealed many authors and journals that have made significant contributions to the field of CRS biomarkers (Fig. 4A). Based on the change in the annual publication volume of the top 10 journals, it showed an overall upward trend in the publication volume of each journal during the period 2003–2022 (Fig. 4B). An overlapped map of the journal was created by CiteSpace to visualize citations of CRS biomarker studies. Figure 4B shows the citation graph on the left, the cited graph on the right, and the curve is the citation path connecting the lines from left to right. (Fig. 4C).
Table 2
Top 10 productive journals in CRS biomarkers from 2003 to 2022

<table>
<thead>
<tr>
<th>Rank</th>
<th>Journal</th>
<th>Number of publications</th>
<th>Proportion H</th>
<th>Total number of Citations</th>
<th>IF (2022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CARDIORENAL MEDICINE</td>
<td>27</td>
<td>4.68</td>
<td>11</td>
<td>616</td>
</tr>
<tr>
<td>2</td>
<td>HEART FAILURE REVIEWS</td>
<td>16</td>
<td>2.77</td>
<td>13</td>
<td>675</td>
</tr>
<tr>
<td>3</td>
<td>JOURNAL OF CARDIAC FAILURE</td>
<td>14</td>
<td>2.43</td>
<td>8</td>
<td>389</td>
</tr>
<tr>
<td>4</td>
<td>JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY</td>
<td>11</td>
<td>1.91</td>
<td>10</td>
<td>2489</td>
</tr>
<tr>
<td>5</td>
<td>INTERNATIONAL JOURNAL OF CARDIOLOGY</td>
<td>10</td>
<td>1.73</td>
<td>7</td>
<td>206</td>
</tr>
<tr>
<td>6</td>
<td>EUROPEAN JOURNAL OF HEART FAILURE</td>
<td>9</td>
<td>1.56</td>
<td>8</td>
<td>663</td>
</tr>
<tr>
<td>7</td>
<td>JOURNAL OF THE AMERICAN HEART ASSOCIATION</td>
<td>9</td>
<td>1.56</td>
<td>7</td>
<td>190</td>
</tr>
<tr>
<td>8</td>
<td>BLOOD PURIFICATION</td>
<td>9</td>
<td>1.56</td>
<td>5</td>
<td>108</td>
</tr>
<tr>
<td>9</td>
<td>SCIENTIFIC REPORTS</td>
<td>8</td>
<td>1.39</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>KIDNEY &amp; BLOOD PRESSURE RESEARCH</td>
<td>7</td>
<td>1.21</td>
<td>6</td>
<td>73</td>
</tr>
</tbody>
</table>

3.5 Author analysis

Over the last 20 years, 3165 authors have contributed to the study of biomarkers of CRS. Among them, the top 10 productive authors have published 135 articles, accounting for 23.40% of the total. Ronco Claudio had the highest number of publications with 42 articles (7.28% of the total), followed by Mccullough, Peter A. with 15 articles (2.60% of the total). In the ranking of authors' citations, Ronco, Claudio ranked first with 3910 citations, and the second-ranked author was Bellomo Rinaldo with 2316 citations. (Table 3) For co-occurrence analysis of authors, Fig. 5A shows the collaborative network among authors, Fig. 5B shows the intensity of collaboration among authors, and Fig. 5C shows the average number of citations of core authors.

3.6 Reference analysis

All cited references form a collection, which is the research knowledge base of a discipline. Co-citation analysis was performed to explore the research hotspots in the field, and a total of 19,743 references were cited in the 577 included publications after analysis. The results of the cluster analysis are shown in Fig. 6A, including 10 major clusters(#0 biomarkers, #1 point-of-care ultrasound, #2 renocardiac syndrome,
#3 decompensated heart failure, #4 nesiritide, #5 renal replacement therapy, #6 extracellular vesicles, #7 mean platelet volume, #8 severe cardiorenal syndrome, #9 anemia). A timeline figure was merged by CiteSpace (Fig. 6B) to visualize the phase changes of each cluster. Citation burst map showed the top 25 burst citations in CRS biomarker studies from 2003–2022 (Fig. 6C).

### 3.7 Keywords Cluster analysis and co-occurrence analysis

A total of 2236 keywords were extracted from 577 papers in the last 20 years, and 234 keywords appeared more than five times. Based on the cluster analysis of keywords, the CRS biomarkers were classified into ten major clusters (#0 cardiovascular disease, #1 peritoneal dialysis, #2 b-type natriuretic peptide, #3 natriuretic peptides, #4 cystatin c, #5 endothelial dysfunction, #6 renal insufficiency, #7 acute heart failure, #8 acute decompensated heart failure, #9 myocardial infarction) (Fig. 7A). The clusters were mainly related to cardiac disease, kidney disease, markers, mechanisms, and treatments. By the figure of keyword co-occurrence (Fig. 7B), the most frequently occurring keyword was cardiorenal syndrome. In addition to the disease-based keywords, pathophysiology-related descriptions were apolipoprotein, glomerular filtration rate, oxidative stress, BNP, and cystatin C, which are hot spots for treatment, mechanism, and diagnosis-related studies of CRS. Descriptive keywords are mortality, outcome, diagnosis, prognosis, and biomarkers. The keyword timeline figure shows the time course of each clustering. (Fig. 7C)

### 3.8 Key words Burst analysis

We used CiteSpace for burst analysis and mapped the top 25 burst keywords in CRS biomarker studies from 2003–2022. In addition to the keywords mentioned above, more keywords in the field of CRS biomarkers were revealed, as shown in Fig. 8.

### 4 Discussion

#### 4.1 General information

Since the research on CRS biomarkers has been initiated, the number of publications is generally increasing, indicating that the field has received continuous attention. According to the fitted model, the number of publications is predicted to be 60 in 2023, which is expected to surpass the number of publications in 2015 and reach another peak. It indicates that the topic of CRS biomarkers has research value and potential for development.

According to the analysis of national contributions, the USA ranks first in publications, citations, and H-index. As the center of the national collaborative relationship network, the USA forms close ties with other countries, indicating that the USA has a dominant position in the field of CRS biomarkers research. It is worth noting that Canada ranks 7th in terms of the number of articles published, but it ranks second in terms of the number of citations and H-index, which may relate to its more refined publications. Although
China is ranked third in terms of the number of publications, its citation volume and H-index have not reached a similar level, which may be related to publication type and language.

Among the top 10 productive institutions, four are from the United States, and three are from Italy, which echoes the results of the national publication ranking. San Bortolo Hosp is ranked first in terms of both publications and citations, with outstanding contributions to CRS biomarker research. Chang Gung Univ is slightly superior to Duke Univ in terms of publications. However, in terms of collaboration, Chang Gung Univ is more closely associated with Asian institutions, while Duke Univ is more closely associated with international ones.

CARDIORENAL MEDICINE (IF = 4.36), the journal with the highest number of publications, is a journal focused on CRS research, with a rapid increase in the number of publications since 2012, much higher than other journals, and has played a crucial and transformative role in the development of CRS research. JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY (IF = 27.203) ranked 4th in terms of the number of articles published. Among the top 10 journals, it is the most cited, far more than other journals. In addition, we found two main citation pathways in the overlapped map of the journal. Studies were mainly published in medicine, medical, and clinical journals, and the sources of cited studies were from two categories (#1 health, nursing, medicine; #2 molecular, biological, and genetic).

In the analysis of author contributions, Claudio Ronco has an absolute advantage over other authors in terms of the number of publications and citations. In addition, the top two citations in the reference analysis were also written by this scholar. He published a review named Cardiorenal Syndrome in 2008, recognizing that although the name CRS disease is gradually being used widely, there is still no accepted definition. To describe the complex pathophysiological association and bi-directionality of the heart and kidney in more detail, he proposed to classify CRS into five categories and elaborated on the name, mechanism, and treatment of each subtype in the review. The role of biomarkers (creatinine, BNP, cystatin C, NGAL, and C-reactive protein) in the early diagnosis, treatment, and prognosis of CRS was also discussed. The definition of CRS and the identification of subtypes were clarified in the ADQI consensus conference report published in 2010. The article focused more on the exploration of each subtype, introducing the epidemiology, biomarker diagnosis, prevention, and treatment options for each subtype of CRS, moreover, the role of imaging in the diagnosis of CRS was proposed. In addition, according to the author’s collaboration network map, Claudio Ronco occupies an equally important position, followed by McCullough, Peter A. and Bellomo, Rinaldo.

### 4.2 Frontiers and Emerging Trends

In the reference clustering, #0 is biomarkers, indicating that the included literature is closely related to biomarkers and consistent with the study topic. #7 is mean platelet volume which is closely related to cardiovascular disease. #9 is anemia, anemia not only has a cardiovascular impact but also can be found in CRS, especially in type 2. Correcting anemia may improve symptoms and may be a useful management strategy. #4 is nesiritide which echoes the keyword clustering results. The timeline figure can reflect the hotspots in each period, and it is possible to see the evolution of CRS research. It started
with the introduction of CRS, goes through the exploration of the definition of the disease, then enters the stage of diagnostic research of the disease (biomarkers, ultrasound testing), followed by the treatment of the disease (renal replacement therapy).

Among the ten major clusters obtained by keyword analysis, #2 b-type natriuretic peptide, #3 natriuretic peptides, and #4 cystatin c clusters are biomarkers. BNP is a kind of natriuretic peptide, which has the function of vasodilatory, cardioprotective, and sodium-removal diuretic. NT-proBNP, as cardiac injury biomarker in CRS, is the preferred marker for the diagnosis of heart failure. It can be used to guide treatment as well as measure efficacy and also has a high ability to assess disease prognosis. Plasma BNP levels were found to be elevated in patients with renal impairment (GFR threshold was 60ml/min). Sofia Sundqvist et al. explored NP as a biomarker to predict the risk and prognostic value of renal replacement therapy in patients with chronic kidney disease (stage 4 and 5) through clinical trials and found that plasma NT-proBNP level was higher in the advanced stage of renal dysfunction. After a five-year follow-up of these patients, it was found that BNP level > 140ng/L was a predictive node for dialysis treatment, and NT-proBNP level > 1345 ng /L was valuable for predicting the survival rate of cardiovascular events. In the NP family, in addition to the above two, new biomarkers are gaining attention, such as the intermediate fragment atrial natriuretic peptidogen (MR-proANP), human adrenal medullary intermediate peptide (MR-proADM) and peptidein. As early as 2007, von Haehling S et al. showed that MR-proANP has good stability and sensitivity through clinical trials, and confirmed its value to be superior to BNP and NT-proBNP, but it is less used at present. Cystatin C is a sensitive marker of renal impairment. Cystatin C is not secreted via the renal tubules. Cystatin C is usually found in low levels in the urine and can reflect tubular damage. Serum cystatin C level is a marker of glomerular filter rate. A prospective study investigated the relationship between cystatin C and CHF, and found that plasma CysC level was significantly increased in CHF patients, and CysC level was closely correlated with the degree of ventricular dysfunction, and could be used as a mortality marker for CRS and HF and independent predictors of long-term prognosis. It has also been shown that cystatin C levels reflect true GFR and are less affected by factors other than renal function. C-reactive protein is a biomarker of acute coronary events that can be independently predicted and it has increased activity in CRS. In addition to the biomarkers shown in the keyword cluster, there are other biomarkers such as serum creatinine (Scr), neutrophil gelatinase-associated lipocalin (NGAL), KIM-1 and CRP. Among them, Scr, NGAL and KIM-1 are the classic biomarker used to evaluate renal function and are also used in CRS. Increased Scr level is one of the main indicators to diagnosis kidney injury, which is widely used in clinic. A meta-analysis showed that NGAL could predict subclinical acute kidney injury at an early stage. KIM-1 is a specific marker of proximal renal tubular injury, and increases within hours after the occurrence of renal injury. Therefore, KIM-1 has the potential to be a rapid detection of ischemic renal injury, with its level peaking ~ 3 days after injury. KIM-1 has also been shown to be elevated in patients with heart failure and is associated with cardiovascular events and mortality in patients with CKD. Danijela Tasic found that CRP levels were elevated in CRS through controlled clinical trial and suggested that CRP may be a valuable marker for clinical differentiation of cardiorenal syndrome types. Cluster “#5 endothelial dysfunction” belongs to
the pathological mechanism of CRS. Endothelial dysfunction is one of the important causes of CKD and HF. It is an early marker of atherosclerosis, and arteriosclerotic vascular disease (ASVD) plays a major role in the pathological link of CRS.\textsuperscript{29,30,31} Cluster \\
"#0 cardiovascular disease #6 renal insufficiency #7 acute heart failure #8 acute decompensated heart failure #9 myocardial infarction" were all CRS-related disease names. Cluster #1 peritoneal dialysis is the treatment method. The time line of each keyword in the cluster is shown in the Fig. 7, reflecting the evolution of each keyword in different periods.

"Burst keywords" are keywords that appear suddenly or frequently during a certain period, reflecting the hot issues and their evolution during that period. Among the top 25 burst keywords related to biomarkers, brain natriuretic peptide (BNP, started in 2003) was the first to appear and continued to be hot for a long time. It was followed by creatinine (started in 2004), and C-reactive protein (started in 2005). BNP and creatinine both ended in 2011, followed by C-reactive protein in 2012. It indicates that these CRS biomarkers were once of great interest, but as research progressed, the era of the "old" biomarkers came to an end and gradually moved toward new markers. The "Burst keywords" in the mechanism category are oxidative stress and fibrosis, which have emerged simultaneously with the type of study and pathophysiology and continue to this day. It indicates that research on CRS is moving toward the exploration of pathological mechanisms and is a hot topic and direction for future research.

There was also a period of enthusiasm for keywords of disease names, starting in 2004–2006, which may be related to the unconfirmed definition of CRS and the proposal of CRS typology by Claudio Ronco scholars, which ended in 2011. Prior to this, the report of the 2010 ADQI Initiative Consensus Conference clarified the concept and typing of CRS. Dialysis (2012–2013) burst once, and then again in 2016. Renal replacement therapy (2017–2018), although bursting for a shorter period, also proved that research on the treatment of CRS never left the limelight. ESC guidelines are catching the eyes of researchers, and the application of biomarkers to the prevention, management, and treatment of the disease will be a hot topic in the future.

5 Conclusion

This study analyzed the publications in the field of CRS biomarkers in the last two decades using bibliometric analysis. Currently, the publications of CRS biomarker-related studies show continuous growth, and more and more new biomarkers are proposed for CRS diagnosis, assessment of efficacy, and prognosis. It indicates that biomarkers are in the hot direction of CRS research. We summarize the contribution as well as collaboration of institutions, journals, and authors, and analyze the research with outstanding contributions and representativeness. Biomarker applications in CRS are receiving more and more attention. Mechanism and pathophysiological exploration have become hotspots for CRS biomarker research, and the value of biomarker in efficacy and prognosis are potential research directions.

It is noteworthy that there are fewer clinical studies on CRS biomarkers. At the same time, the application of biomarkers in clinical diagnosis and prognosis is also low, and more clinical studies are needed to fill this evidence base. Overall, the bibliometric analysis conducted in this paper provides a more
A comprehensive review of the progress of CRS biomarkers to a certain extent, analyzing the current status, hotspots, frontiers, and future trends in research. It provides some valuable information for researchers who are studying or will join the field of CRS biomarkers.

**Declarations**

- **Ethics approval and consent to participate**
  - Not applicable
- **Consent for publication**
  - Not applicable
- **Availability of data and materials**
  - All data generated or analyzed during this study are included in this published article and its additional information files.
- **Conflict of Interest**
  - The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- **Author Contributions**
  - Xinxin Mao conceived wrote the article. Haoran Zheng and Zhenyue Fu did the mapping. Jiayu Lv, Shuqing Shi, et al. retrieved and organized documents. Qingqiao Song, Huaqin Wu, Bingxuan Zhang had an outstanding contribution in second-time revision, polishing the manuscript and helping in revising figure.
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**References**


Figures

A

Annual publications of studies related to cardiorenal syndrome biomarkers from 2003 to 2022.

B

\[ y = 2.8714x \]
\[ R^2 = 0.953 \]

C

Review: 24.96%

Article: 75.04%

Figure 1

Annual publications of studies related to cardiorenal syndrome biomarkers from 2003 to 2022.
A: The change in the number of annual publications; B: The trendline of the number of annual publications; C: The percentage of publication types

Figure 2

Major countries/regions for studies related to cardiorenal syndrome biomarkers from 2003 to 2022.

A: Major countries/regions distribution characteristics map; B: Publications radar map of major countries/regions; C: Citations radar map of major countries/regions; D: H index radar map of major countries/regions
Figure 3

Major institutions for studies related to cardiorenal syndrome biomarkers from 2003 to 2022.

A: Collaborative network map of major institutions; B: Trends in the number of annual publications of institutions.

Figure 4

Major journals for core-related research on CRS biomarkers from 2003 to 2022.

A: Domain graph of authors, keywords, and source journals; B: Overlapped graph of source journals and cited journals; C: Trends in the number of annual publications of journals.
Figure 5

Visualization of author co-occurrence network mapping for CRS biomarker studies from 2003 to 2022.

A: Collaboration network map of authors; B: Collaboration intensity network map of authors with more than 5 publications; C: Core author collaboration network overlaid with citation count map
Figure 6

Reference visualization analysis mapping of CRS biomarker studies from 2003 to 2022.

A: Reference clustering; B: Reference clustering timeline; C: Top 25 burst citations
Figure 7

Keyword visualization analysis mapping of CRS biomarker studies from 2003-2022.

A: keyword clustering; B: keyword co-word analysis; C: keyword clustering timeline
### Top 25 Keywords with the Strongest Citation Bursts

<table>
<thead>
<tr>
<th>Keywords</th>
<th>Year</th>
<th>Strength</th>
<th>Begin</th>
<th>End</th>
<th>2003 - 2022</th>
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### Figure 8