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Bibliometric analysis of levosimendan

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ABSTRACT

Background: Levosimendan (LEVO), a calcium sensitizer and adenosine triphosphate-dependent potassium channel opener, has been widely used for decades in medical and surgical patients for advanced heart failure (HF), right ventricular failure, cardiogenic shock, takotsubo cardiomyopathy, pulmonary hypertension, and so on. Currently, as the limited scope and lack of comprehensive data in current LEVO publications, there is an increasing obstacle to conducting new studies that require integrated information and quantifiable results. Thus, the current study was performed to identify the research trends and hot spots in LEVO-related publications using bibliometric software.

Methods: LEVO-related publications from 1990 to 2023 were searched and retrieved in the Web of Science Core Collection (WoSCC) and analyzed with VOSviewer, CiteSpace, Scimago Graphica, R-bibliometrix and Rstudio for publication dates, countries/regions, institutions, authors, keywords, journals, and references.

Results: Finally, a total of 1,432 LEVO-related articles were included in the present study. Annual LEVO-related publications have been increased yearly. The United States was the most productive country with 243 articles. The University of Helsinkin published 69 articles in the field of LEVO, which were the most productive institution among all the institutions. Of all the authors, professor Pollesello,Piero was the most productive author with 62 articles. Moreover, the results of the co-citation analysis and citation bursts analysis revealed that the safety and effectiveness of LEVO were the global research trends and potential hot spots.

Conclusions: This study systematically summarizes the current status in the field of LEVO and provides insights into the research focuses and future hotspots.

1. Introduction

Levosimendan (LEVO), was developed in the early 1990s in Finland and was first approved by Swedish regulatory authorities in 2000 for expanding treatment options for patients with acute heart failure (AHF) or acutely decompensated heart failure (ADHF) [1–4]. In the ensuing years, the clinical application of LEVO had expanded considerably, both in the medical and the surgical settings.

LEVO, which is a distinctive inodilator, exerts its inotropic effect *via* binding to the Ca^{++} saturated troponin C of the myocardial thin filament and promotes systemic vasodilatation at usual therapeutic doses through the opening of ATP-dependent potassium (K_{ATP}) channels in vascular smooth muscle cells [5,6]. LEVO could also open K_{ATP} channels in mitochondria, exerting potentially cardioprotective effects [7–10].

Additionally, LEVO has a range of ancillary actions including anti-inflammatory effects [11–13], antiapoptotic effects [14,15]. It has also been reported that LEVO could affect platelet function [16–18]. All these indicate the pleiotropic properties of LEVO on multiple tissues through various underlying mechanisms. Besides LEVO in IV formulation used as a research tool in the exploration of a wide range of cardiac and noncardiac disease states, a LEVO oral form is at present under evaluation in the management of amyotrophic lateral sclerosis, which might help accelerate the development of novel therapeutic applications for this multifaceted drug [2].

Currently, as the majority of the LEVO publications are in-depth studies on molecular mechanisms and clinical application, most articles on LEVO have focused not only on specific but also relatively limited aspects like pharmacological activities or pharmacokinetics

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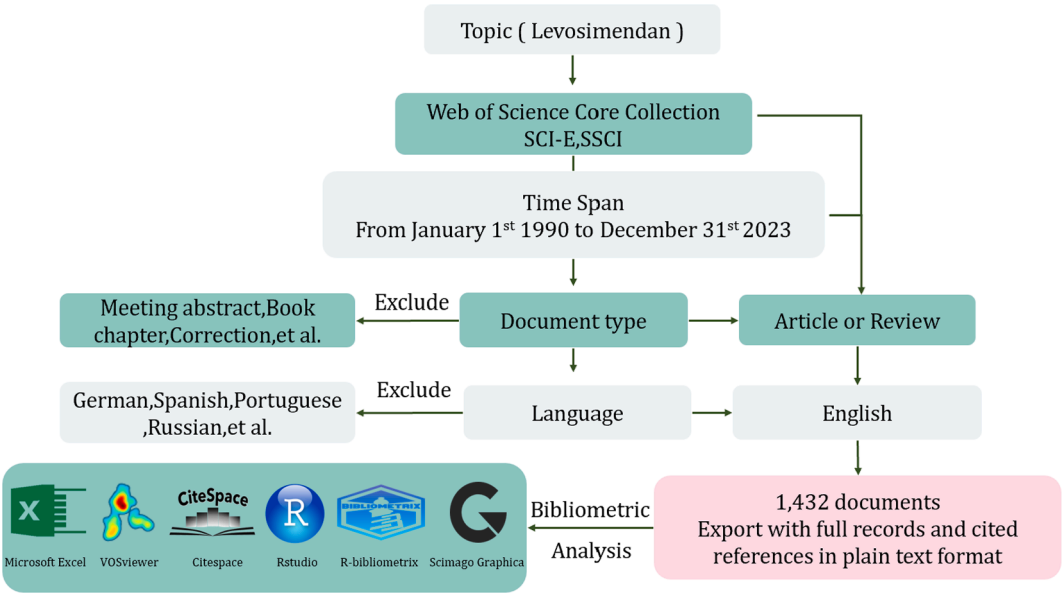

Fig. 1. Flowchart of study identification and selection based on Web of Science.

characteristics[19,20]. Thus, there is an increasing difficulty of carrying out new studies due to the insufficient integrated data or traditional reviews with limited quantification and repeatability.

The purpose of this study was to build up essential, reliable, and thorough information on LEVO since its early emergence. To achieve this, a bibliometric analysis summarizing key information on authors, institutions, literatures, and their interrelationship from database were used. We hope to gain a deeper understanding of current hot areas and extend the current and strong discussion around the potential research directions.

2. Methods

2.1. Data sources and documents collection

2.1.1. Sources of data and search strategy

Regarded as the most influential database for scientific research, the WoSCC (Web of Science Core Collection) covers a wide range of publications from different fields. So the literature of this bibliometric analysis study was obtained from the Science Citation Index Expanded (SCI-E) and the Social Science Citation Index (SSCI) of the WoSCC. Moreover, the search formula was set to topic = ("Levosimendan"), the document type was set as "Articles" OR "Review articles", the publication time was limited to a period from January 1st 1990 to December 31st 2023 and the language was set as "English".

2.1.2. Article screening

The data were collected on May 19th, 2024, and 2,467 original articles were obtained from the WoSCC. Two researchers (Z.X.S, Y.Y.P.) independently screened the literature, and differences were resolved by consensus with the senior researchers (Y.Y.T.). After the screening, 1,432 articles were included in this analysis, while 1,035 articles were excluded because they did not meet the requirements: Citation indexes were not "SCI-E"、"SSCI", the document type was not "Article" or "Review", and the language is not "English".The research characteristics of these publications were shown in Fig. 1.

2.2. Bibliometric analysis

The data to be studied, such as yearly number of publications, and number of articles published by countries/regions, institutions, authors, journals, keywords, and references were downloaded from WoSCC.

Additionally, the impact factor (IF) and quartile in the category of journals were obtained from the 2022 Journal Citation Reports to evaluate the scientific influence of the journal.

VOSviewer, developed by the Centre for Science and Technology Studies at Leiden University, is the most frequently used bibliometric analysis tool, which can construct networks of countries/regions, institutions, journals, researchers, and individual publications based on citation, bibliographic coupling, co-citation, or co-authorship relations [23].

It is especially useful for displaying large bibliometric maps in an easy-to-interpret way. In this study, this software was used to perform (1) countries/regions co-authorship, (2) institutions co-authorship, (3) journals citation and co-citation, and (4) authors co-authorship and co-citation.

Citespace is a piece of software that visualizes networks among collaboration and document citations as well as research hotspots, which visually map highly cited and pivotal documents, areas of specialization within a knowledge domain, and the emergence of research topics [24–26].

In this study this software was used to (1) detect a citation-burst analysis of references, (3) generate the dual-map overlay of journals, (2) generate the visualization map of references and the visualization map of references cluster.

Apart from the above methods, the R-bibliometrix tool was used to

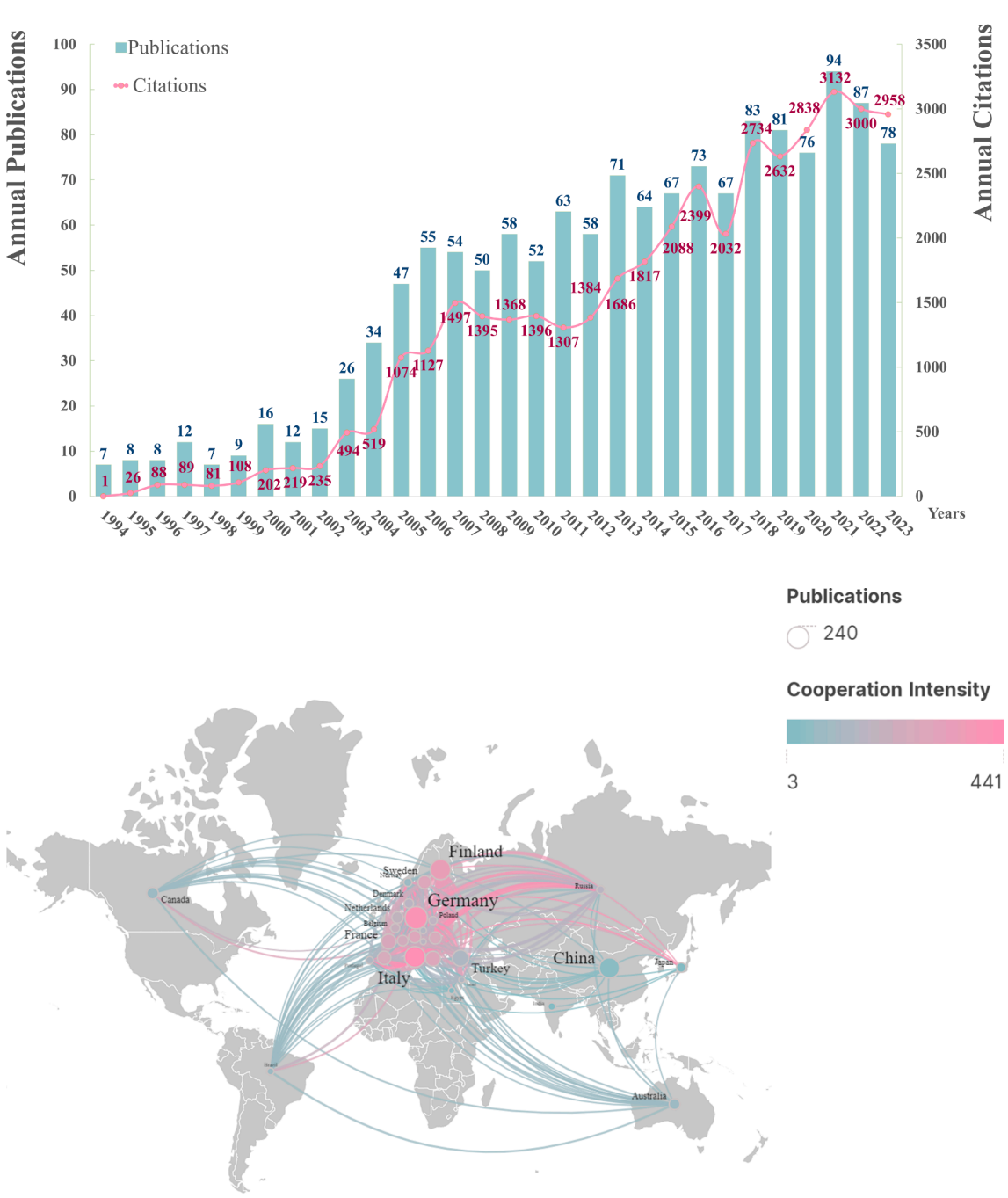

Fig. 2. Overview of publications around the world by 2023. (A) Timeline of publications and citations on LEVO; (B) World atlas of publications in different countries and relationships among the countries. The size of the circle and the font size in the world map indicates the number of publications. The lines between countries means the countries cooperate with each other; (C) Network evaluating international collaborations; (D) The annual citation number and the annual H-index of publications.

(1) analyze the type of publication, whether single country publication or multiple country publication, (2) assess the individual authors' productivity with Lotka's law, (3)detect the most relevant publication sources with Bradford's law.

The Scimago Graphica tool was used to perform collaboration network between countries/regions. The panels of visualization of the timeline view of the author's publication and keywords were constructed using R packages (ggplot2, bibliometrix). Other graphs were created using the Microsoft Excel software.

2.3. Lotka's and Bradford's law

The author's productivity was examined by using Lotka's law, which can demonstrate the relationship between the number of authors and the number of contributions made by each author.[37]

Lotka's law is expressed in mathematical terms by the following formula:

$$A(n) = \frac{A(1)}{n^2}$$

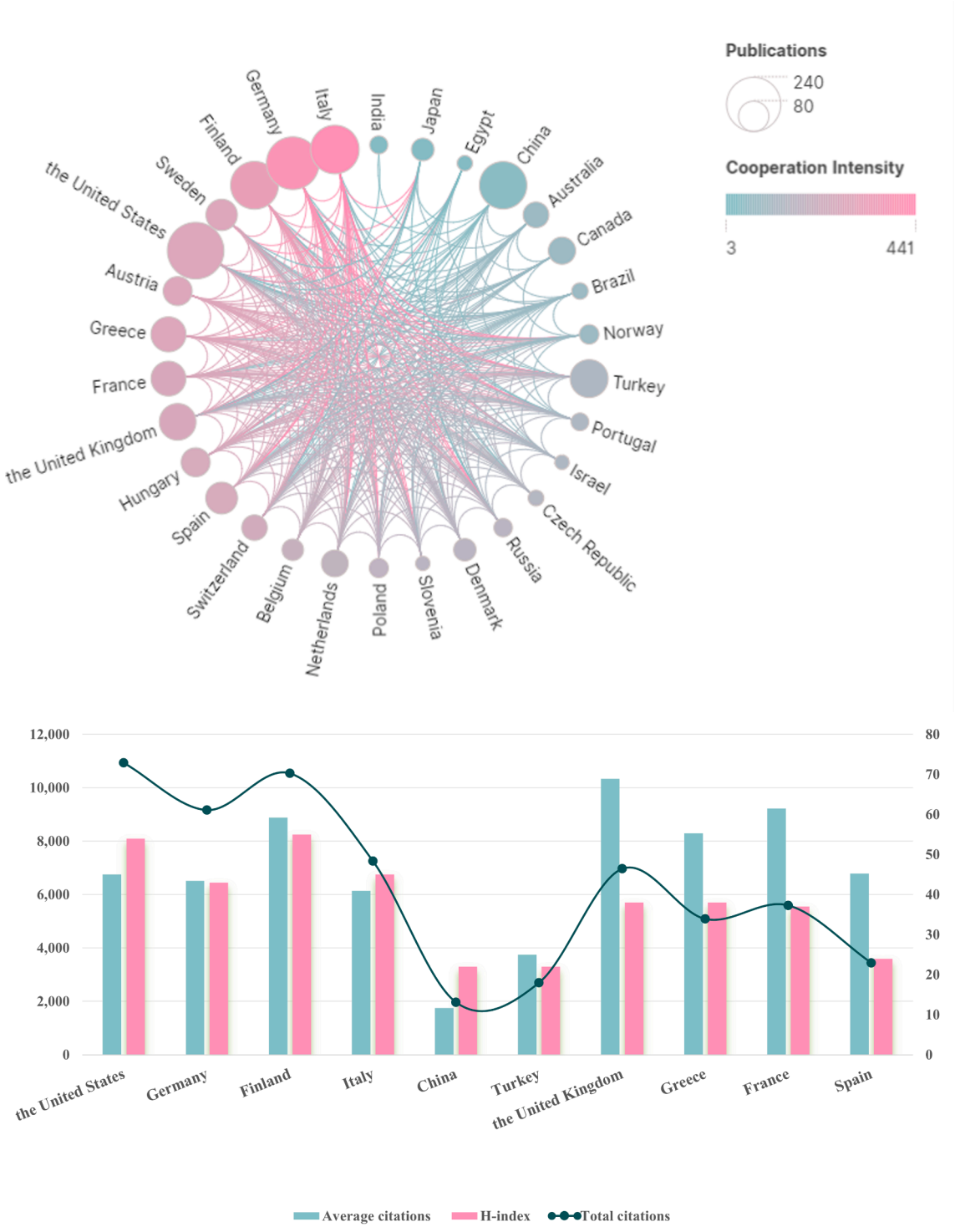

Fig. 2. (*continued*).

In the above equation, A (n) is the number of authors publishing n papers and A (1) is the number of authors publishing a single paper.

Bradford's law was used to detect the most relevant publication sources, distributing the journals into zone 1 (core journals), zone 2, and zone 3.

3. Results

3.1. Global overview of publications in LEVO by the end of 2023

A total of 1,432 articles were included in our study. The first study in the field of LEVO was traced back to 1994. With the fast development

Table 1
Top 10 contributing countries of LEVO publications.

Rank	Country	Total publications	Total citations	Average citations	H-index
1	United States	243	10,933	44.99	54
2	Germany	211	9,165	43.44	43
3	Finland	178	10,539	59.21	55
4	Italy	177	7,252	40.97	45
5	China	168	1,963	11.68	22
6	Turkey	108	2,697	24.97	22
7	United Kingdom	101	6,963	68.94	38
8	Greece	92	5,085	55.27	38
9	France	91	5,592	61.45	37
10	Spain	76	3,439	45.25	24

and continuous research interests of LEVO, the annual publications have kept a general upward trend. (Fig. 2**A**).

During the studied time period, LEVO-related articles were mainly from America, Europe, and the East Asia (Fig. 2**B**). And the characteristics of the top 10 active countries are shown in Table 1. Of these, the United States, Germany, and Finland were the most productive countries, of which the United States published 243 articles, Germany published 211 articles, and Finland published 178. Fig. 2**D** showed that the three countries both owned high citations and H-index values, which proved their significant scientific influence of them in this field.

The analysis of the country of corresponding author showed that China, the United States, Germany, Finland, and Italy were the top 5 active countries in LEVO-related filed, and Finland showed relatively high international collaboration among them (Fig. 2**C,** Fig. 3**A**). Subsequent network correlation analysis confirmed that Italy, Germany, and Finland had the most active international collaboration in LEVO-related research (Fig. 3**B, C**).

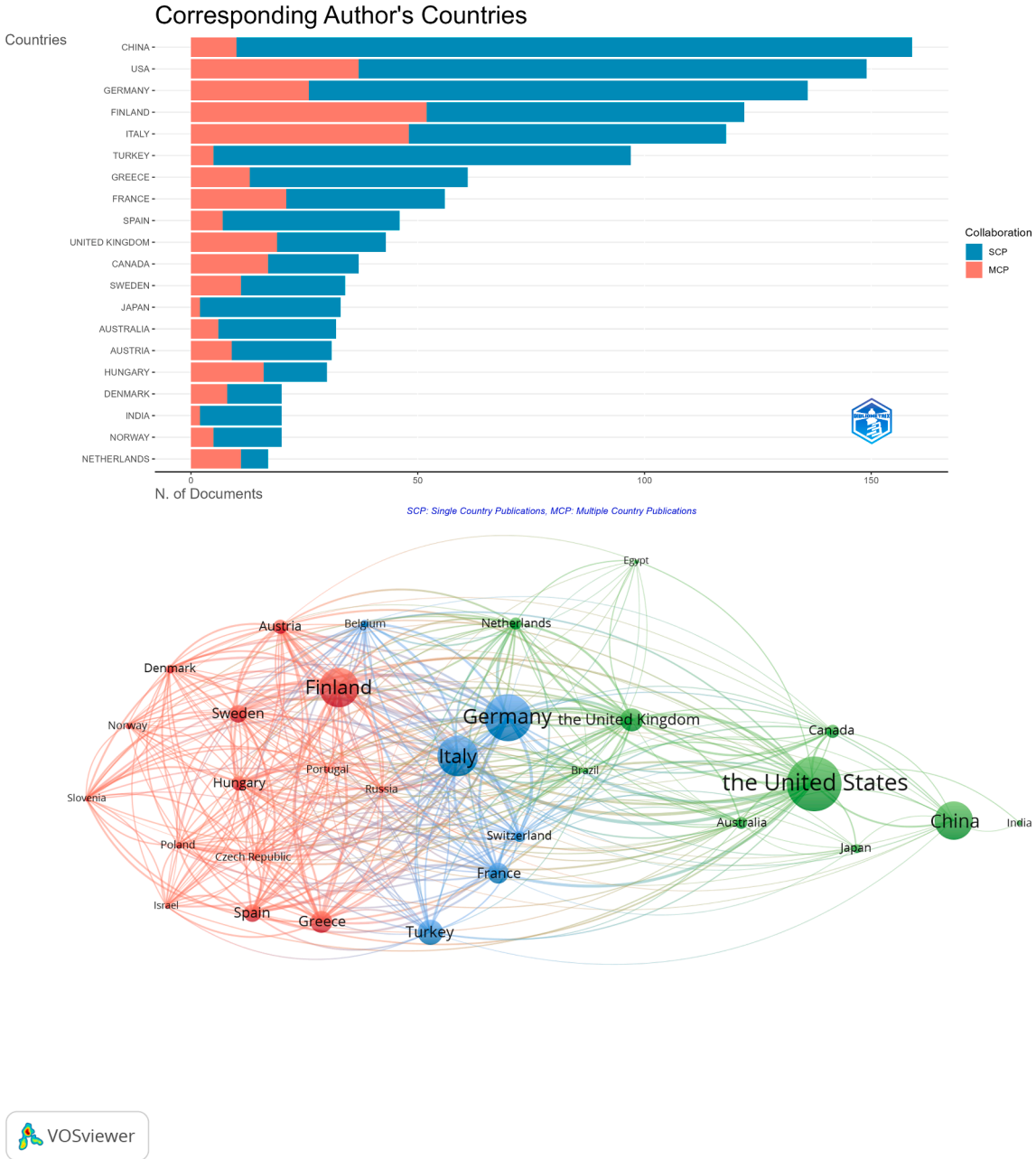

Fig. 3. Country analysis. (A) Corresponding author's countries; (B) Network map of co-authorship country; (C) Density map of co-authorship country.

Fig. 3. (*continued*).

Table 2
The top 10 institutions that contributed publications on LEVO.

Rank	Institutions	Country	Total publications	Total citations	Total Link Strength
1	University of Helsinkin (Univ Helsinki)	Finland	69	5,021	55
2	Orion Pharma	Finland	67	4,896	78
3	The National and Capodistrian University of Athens (Univ Athens)	Greece	32	1320	8
4	University of Alberta (Univ Alberta)	Canada	26	670	22
5	Sapienza University of Rome (Univ Roma La Sapienza)	Italy	26	1,415	26
6	University of Debrecen (Univ Debrecen)	Hungary	25	1,001	40
7	Università Vita-Salute San Raffaele (Univ Vita Salute San Raffaele)	Italy	24	1,394	27
8	University of California, San Francisco (Univ Calif San Francisco)	United States	20	2,110	15
9	Irccs San Raffaele Sci Inst	Italy	17	484	15
10	Duke University (Duke Univ)	United States	16	1,546	23

Researches among European countries were relatively compact, and international cooperation with other countries needed to be strengthened (Fig. 3**B, C**).

3.2. Institutions analysis

Table 2 showed the top 10 institutions in terms of publication number, total citations, and total link strength. The University of Helsinkin topped the list with a total 69 publications and 5,021 citations, followed by Orion Pharma (67 publications), The National and Capodistrian University of Athens (32 publications), University of Alberta (26 publications), and Sapienza University of Rome (26 publications).

The cooperation network showed that the Orion Pharma owned a much greater influence on LEVO-related research than any other

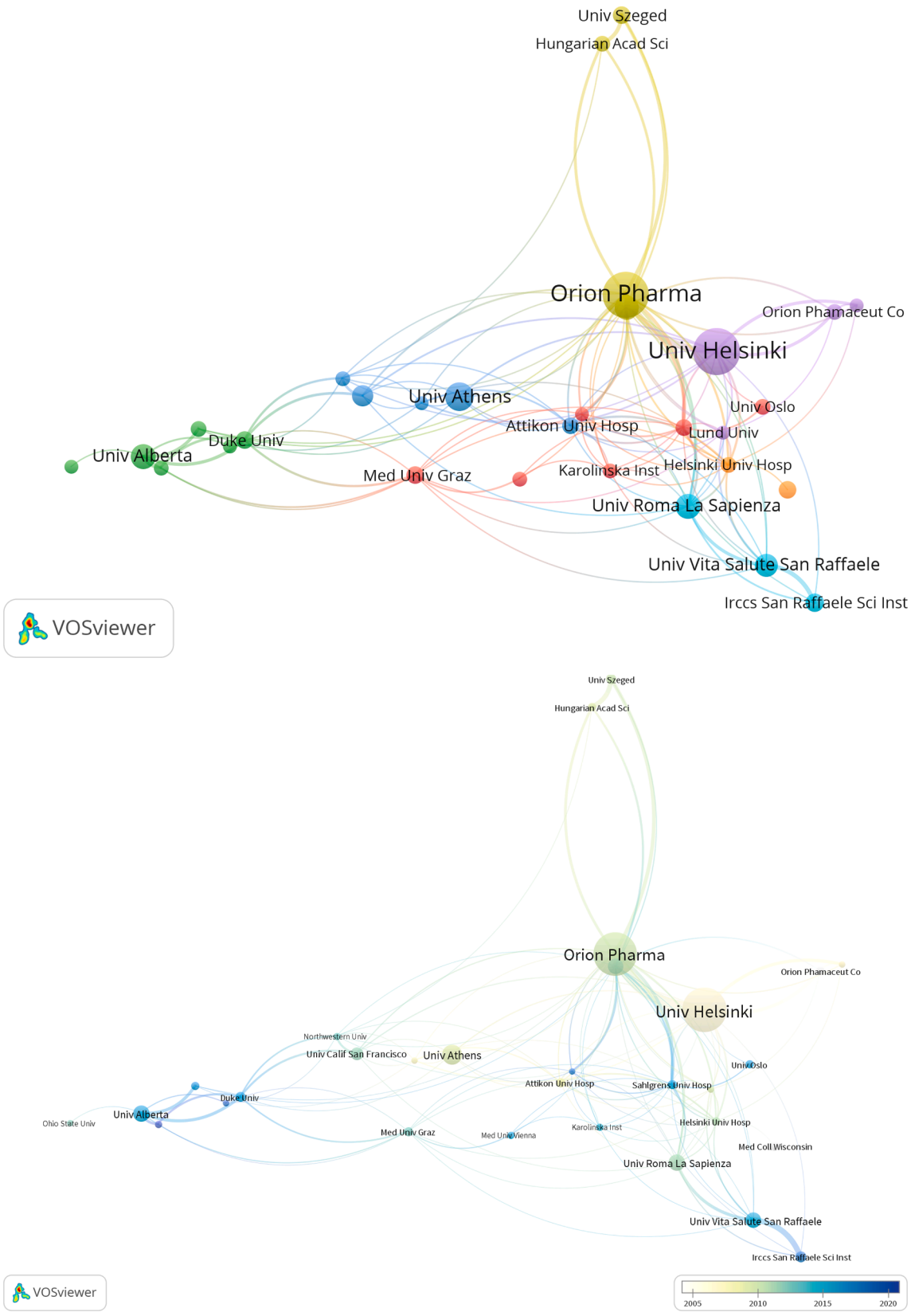

Fig. 4. Institution analysis. (A) Network map of interinstitutional cooperation; (B) Dynamic graph of temporal trends of articles published in the LEVO field; (C) Density map of co-authorship institution.

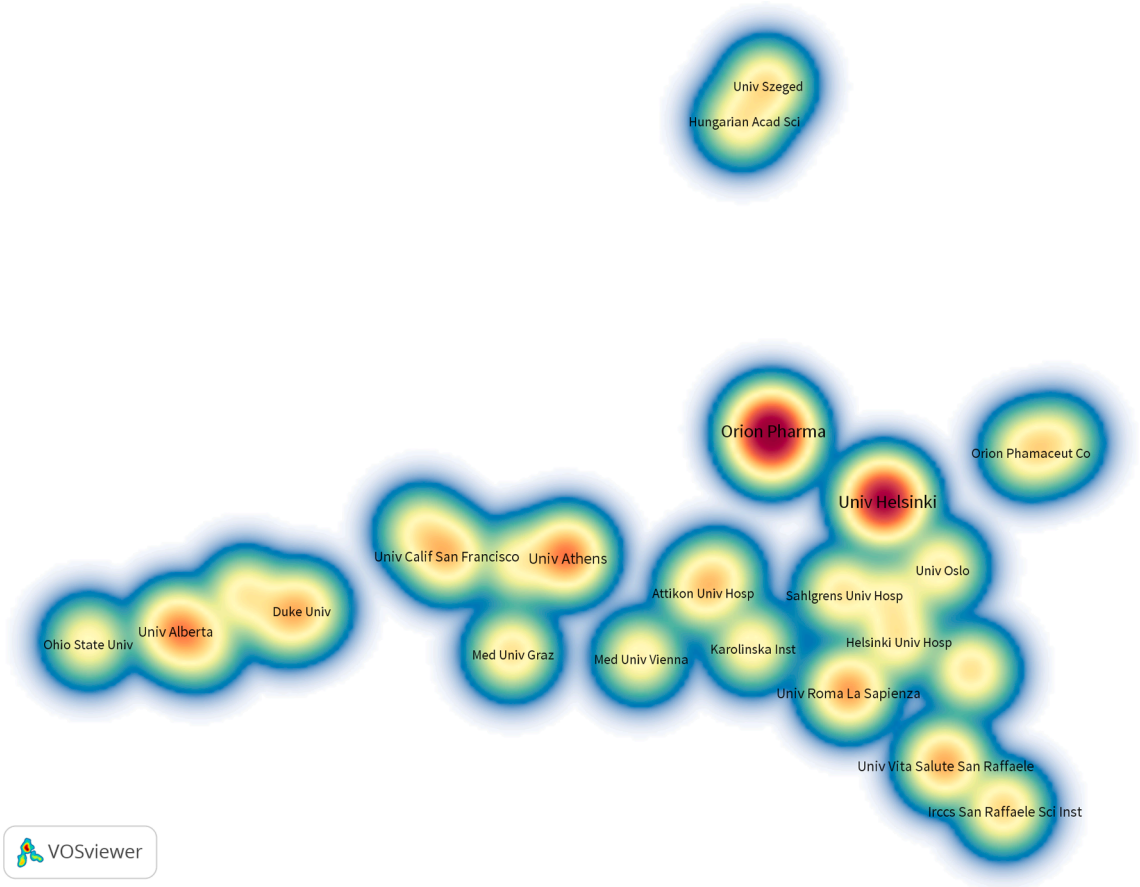

Fig. 4. (*continued*).

Table 3
The top 10 authors that contributed publications on LEVO.

Rank	Authors	Total publications	Total citations	Total link strength
1	Pollesello, Piero	62	2,581	161
2	Lehtonen, La	32	3,334	91
3	Kivikko, Matti	28	2,286	99
4	Mebazaa, Alexandre	28	2,595	61
5	Parissis, John T.	27	1,560	80
6	Levijoki, Jouko	24	1,281	55
7	Landoni, Giovanni	22	1,249	56
7	Nieminen, Markku S.	22	2,262	57
7	Papp, Zoltan	22	896	71
8	Antila, Saila	19	885	36
8	Haikala, Heimo	19	1,419	48

institutions, and the cooperation network also showed that the cooperation among institutions was mostly limited to their respective countries/regions while international cooperation was rare (Fig. 4**A, C**). The network analysis also showed that in recent years, articles in the LEVO field mainly came from Italy, Canada, and the United States (Fig. 4**B**).

3.3. Contributions of authors

Based on the number of publications, we identified the 10 most influential authors of LEVO research (Table 3). The top five most productive authors were professor Pollesello, Piero (published 62 articles), followed by professor Lehtonen, La (published 32 articles), professor Kivikko, Matti (published 28 articles), professor Mebazaa, Alexandre (published 28 articles), and professor Parissis, John T. (published 27 articles).

Based on this collaborative map (Fig. 5**A**), we identified several key research teams (Pollesello, Piero; Kivikko, Matti; Parissis, John T.) and found that all of them had close cooperation. To observe the publications of the professors over time, we conducted further analysis, selected the top 14 authors with overall publications, and visualized the data (Fig. 5B). The authors with the corresponding clusters in Fig. 5A showed different trends, which were roughly classified into rise, fall, and stabilization. For instance, in 1994, Professor Pollesello, Piero published the first paper in the field of LEVO, which continued to rise before 2010. The productivity of authors was analyzed using Lotka's law, as shown in Fig. 5C. The pattern of the number of publications follows Lotka's law.

3.4. Contributions of journals

Table 4 listed the 10 most active journals and the 10 most influential journals in the field of LEVO research. Most of the top 10 active journals belonged to the United States. The top 3 active publications from 1994 to 2023 were *Journal of Cardiothoracic and Vascular Anesthesia*, *Journal of Cardiovascular Pharmacology,* and *International Journal of Cardiology*.

Moreover, in these journals, *European Journal of Heart Failure*, *Critical Care*, *Critical Care Medicine,* and *European Journal of Pharmacology* were ranked in Q1 in the Journal Citation Report quartile. Subsequent network analysis further confirmed these journals' strong influence on LEVO research (Fig. 6).

International Journal of Cardiology, Cardiovascular Drugs and Therapy, and *Journal of Clinical Medicine* were ranked in Q2. *Journal of Cardiovascular Pharmacology* and *Journal of Cardiothoracic and Vascular Anesthesia* were ranked in Q3. This result proved that articles in this field had high quality and were generally recognized by peers.

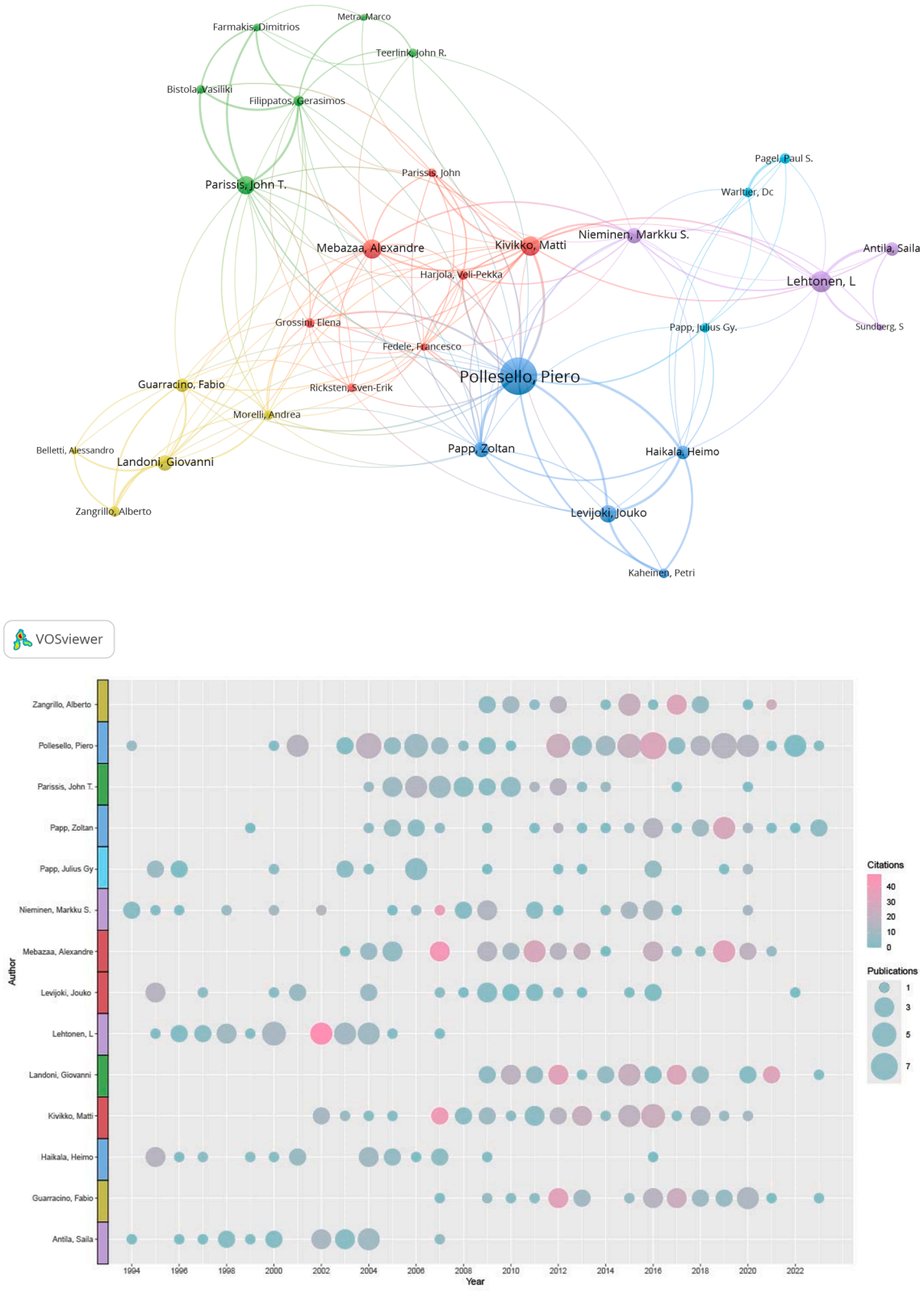

Fig. 5. Overview of co-authorships around the world. (A) Network map of author collaboration; (B) Top 14 authors' publications over time. The different color indicates the corresponding cluster of A. The size of the circle in the line chart refers to the number of publications, and the depth of the round color represents the number of citations. (C) Lotka's law of authors involved in LEVO research. Solid black line indicates the distribution of published articles according to Lotkaw's law. The dotted line indicates the publication on subject matter.

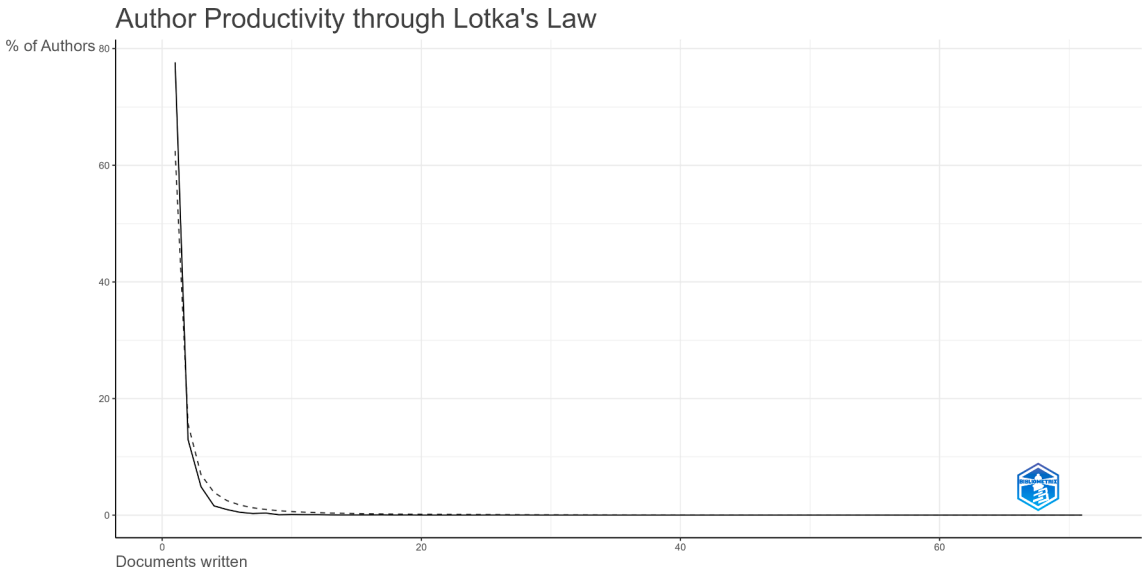

Fig. 5. (*continued*).

Table 4
Top 10 active journals and top 10 influential journals in the field of LEVO.

Journal	Articles	Country	JCR	IF	Co-cited journal	Co-citations	Country	JCR	IF
Journal of Cardiothoracic and Vascular Anesthesia	51	United States	Q3	2.8	Circulation	3,147	United States	Q1	37.8
Journal of Cardiovascular Pharmacology	51	United States	Q3	3.0	Journal of the American College of Cardiology	1,967	United States	Q1	24.4
International Journal of Cardiology	34	Ireland	Q2	3.5	New England Journal of Medicine	1,931	United States	Q1	158.5
European Journal of Heart Failure	29	Netherlands	Q1	18.2	Critical Care Medicine	1,847	United States	Q1	8.8
Critical Care	26	United Kingdom	Q1	15.1	Journal of Cardiovascular Pharmacology	1,774	United States	Q1	3.0
Critical Care Medicine	25	United States	Q1	8.8	European Journal of Heart Failure	1,564	Netherlands	Q1	18.2
European Journal of Pharmacology	22	Netherlands	Q1	5.0	European Heart Journal	1,496	United Kingdom	Q1	39.3
Cardiovascular Drugs and Therapy	27	United States	Q2	3.4	American Journal of Cardiology	1,202	United States	Q3	2.8
Acta Anaesthesiologica Scandinavica	18	Denmark	Q4	2.1	Intensive Care Medicine	1,159	United States	Q1	38.9
Journal of Clinical Medicine	18	Switzerland	Q2	3.9	Lancet	1,080	United Kingdom	Q1	168.9

Furthermore, the citations of *Circulation* and *Journal of the American College of Cardiology* were relatively high, indicating that the manuscripts published in these two journals were of high quality and well-recognized by peers.

The document sources (journals) were divided in to three zones, zone 1 had 25 journals, as shown in Fig. 6B.

The dual map overlay of journals showed two main citation paths: green and orange (Fig. 7). The two paths indicated that papers published in Molecular/Biology/Immunology or Medicine/Medical/Clinical journals usually cited papers published in Molecular/Biology/Genetics and Health/Nursing/Medicine. This result provided a certain reference for new researchers who began to research in this field.

3.5. Keyword analysis

Keyword analysis indicates hotspots and trends in a research field. As shown in Fig. 8A, the most appeared keywords were levosimendan, dobutamine, calcium sensitizer, heart-failure, mortality, efficacy, safety, dysfunction, cardiac troponin-c, milrinone. Based on Fig. 8B, the biggest node is levosimendan, which is same as research topic. This includes three main aspects: pharmacology, the basic clinical application of LEVO, and extended clinical application of LEVO, exhibiting a complex relationship. Over time, the research on levosimendan has changed from focusing on the pharmacological mechanism to studying its clinical application. Clinical application studies are also paying more attention to its effectiveness and safety, as shown in Fig. 8C. Research hotspots have dynamically changed with the application of LEVO. To visualize the distribution of 30 high-frequency keywords across time, we used R packages (bibliometrix, ggplot) to present the keyword distribution from 1990 to 2023(Fig. 8D). For example, from 1994 to 2023, “calcium sensitizer” appeared more frequently in 1995 and less frequently in 2008. In 1994, the more frequent keywords were inotropes and milrinone. Milrinone, a PDE-III inhibitor with inotropic, lusitropic, and vasodilatory properties, was used for the short-term treatment of acute

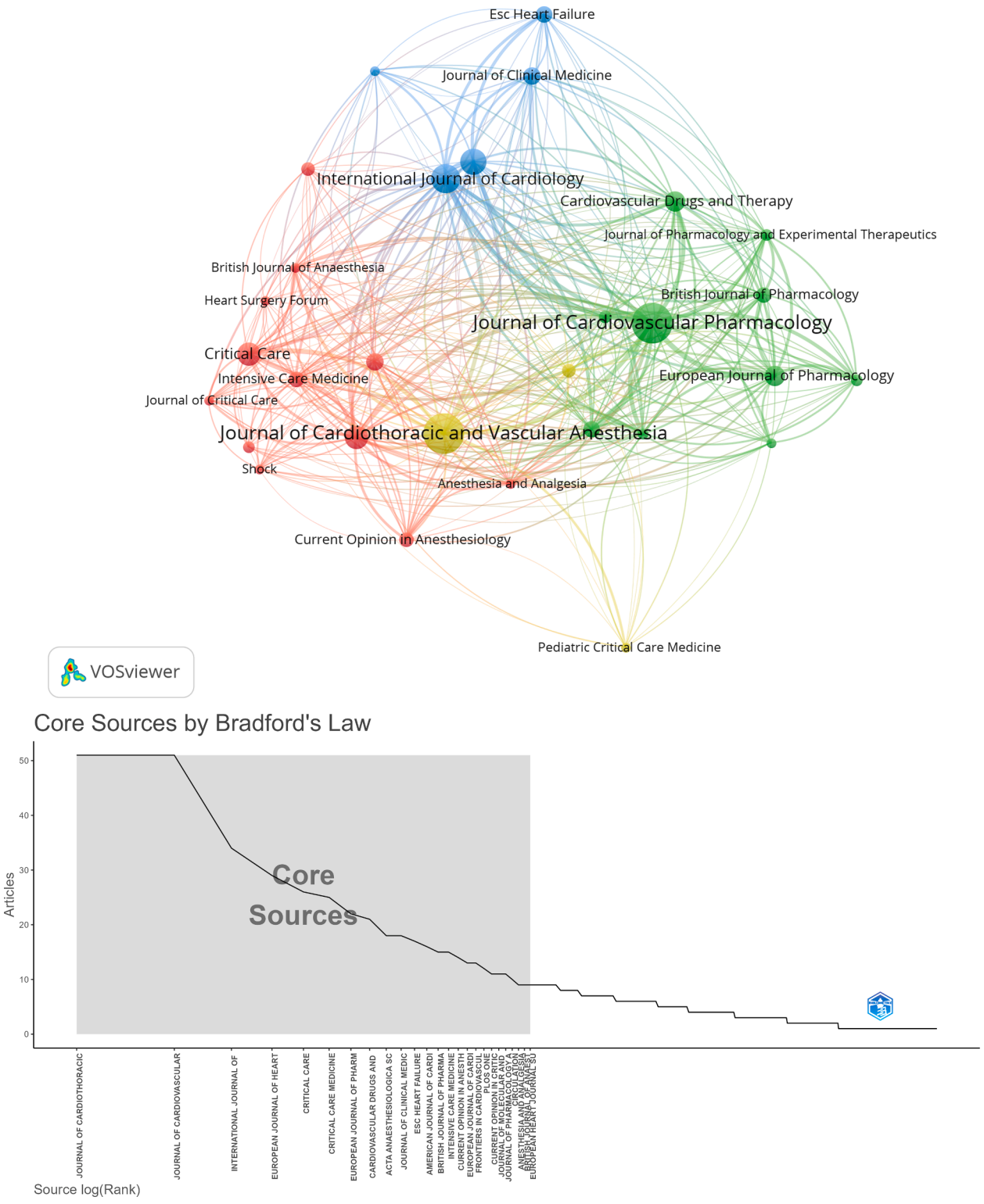

Fig. 6. Journal Analysis. (A) Visualization map of co-cited journals; (B) Bradford's law of journals involved in LEVO research.

decompensated heart failure. Due to the inotropic effects of milrinone and LEVO, it is often used as a control drug in studies evaluating the efficacy of LEVO in the treatment of heart failure. In 2023, the more frequent keywords are shock, cardiopulmonary bypass, pulmonary hypertension, inotropes, and heart failure.

Keyword emergence is shown in Fig. 8E (R packages: bibliometrix, ggplot). As a supplement to keyword co-occurrence analysis, emergent word analysis demonstrates how the research hotspots of LEVO change over time. We analyzed the keywords that are still emerging in 2023, such as "cardiogenic shock," "norepinephrine," "extracorporeal membrane oxygenation," and "acute kidney injury." The research on the safety and efficacy of LEVO, along with the optimal approach for its utilization are still hot spots.

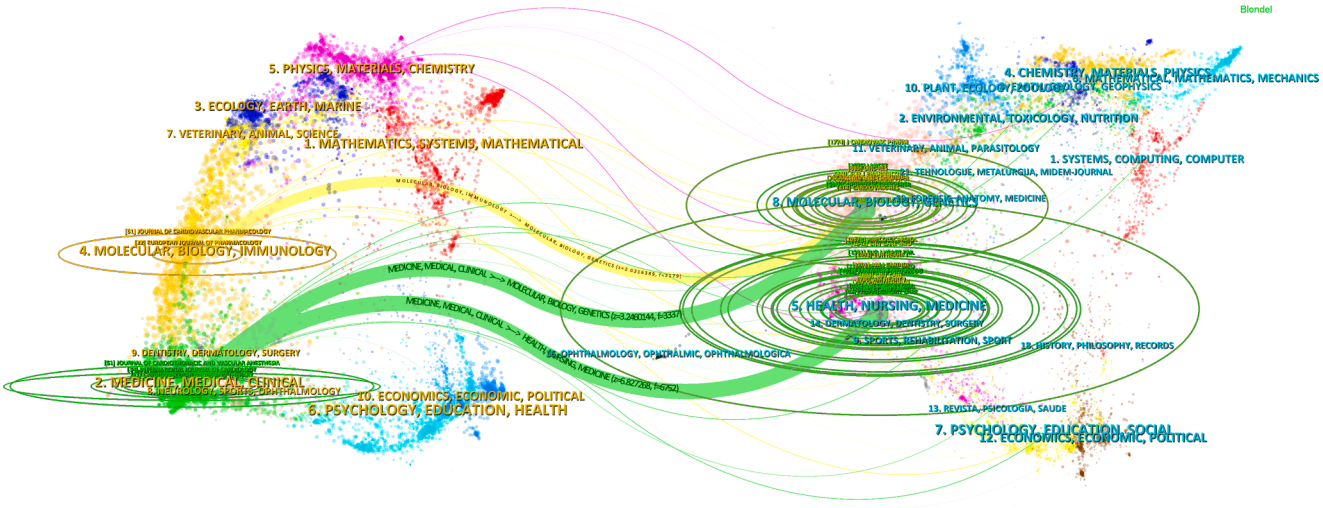

Fig. 7. The dual-map overlay of journals.

Fig. 8. Research focuses and keywords burst by 2023. (A)Word cloud; (B) Visualization map of keywords. Node size and color represents the number of keywords and cluster. Lines of different colors show that the 2 keywords appear in an article ; (C) Dynamic graph of temporal trends of keywords in the LEVO field; (D) Keyword heat map and emergence. The frequency of keyword occurrence was processed by standardization, and the values were distributed between 0 and 1, where each little cell shows the frequency of occurrence of a term in one year. The value of the blue cell is the smallest, representing the lowest frequency of keyword occurrence this year. With the color change, the value of the pink cell is the largest, and its corresponding keyword has the highest frequency of occurrence this year. (E) Keywords with the strongest citation bursts. The blue cell indicates when keyword bursts were detected, and the pink cell displays the time interval.

3.6. Co-cited articles and co-cited reference cluster analysis

Literature co-citation analysis is vital to trace the scientific frontiers and research basis.

Co-citation relationship indicates that two or more articles are cited by one or more articles at the same time, which has been widely used as a research method to assess the degree of relationship between different articles. Therefore, we constructed co-citation correlation and cluster network map by using Citespace software. The most frequently cited references were shown in Fig. 9**A**、**B.**

For the cluster map, we found that the seven hot spots on LEVO research: #0 “acute heart failure syndrome,” #1 “conscious dog,” #2 “clinical evidence,” #3 “acute heart failure,” #4 “undergoing cardiac surgery,” #5 “advanced heart failure,” 6# “septic shock.” (Fig. 10**A**).

Co-cited reference cluster dependencies analysis showed the evolution of the theme in LEVO field (Fig. 10B). Some clusters build on several

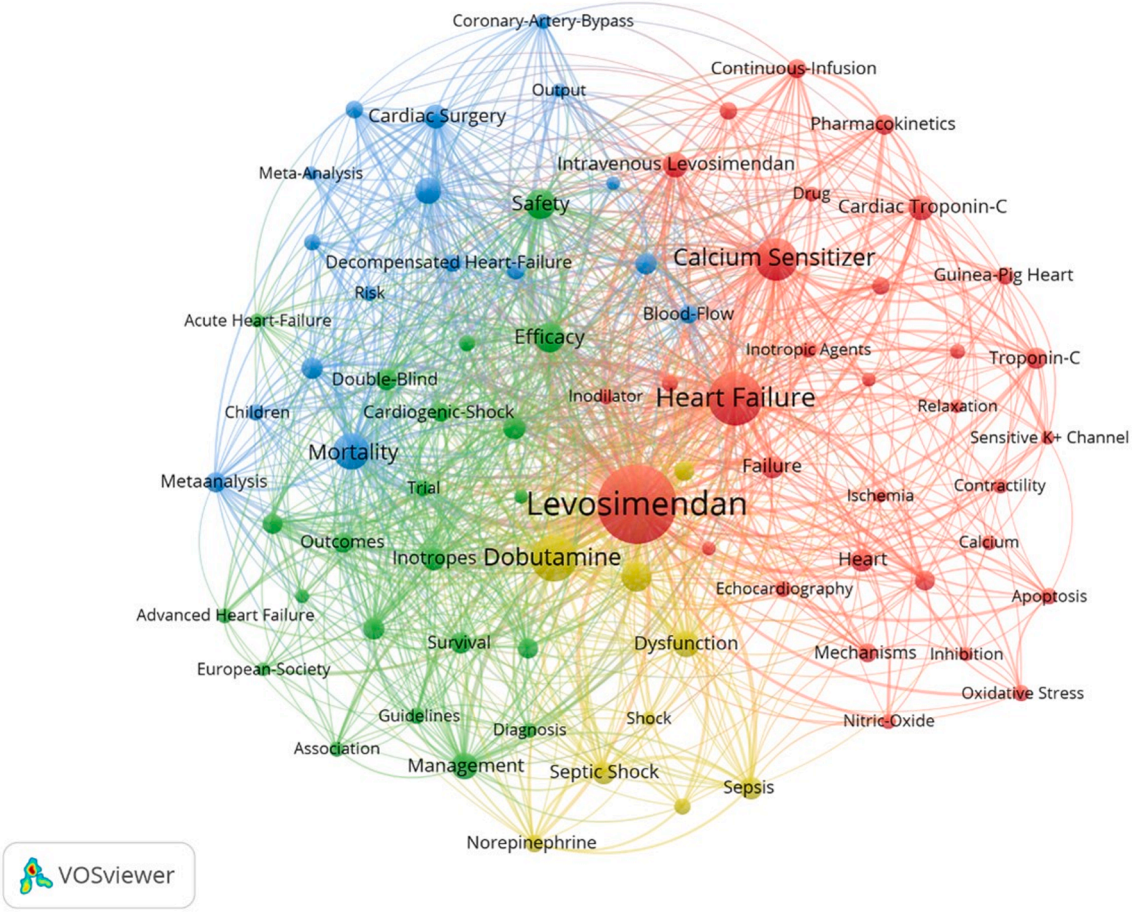

Fig. 8. (*continued*).

other clusters, and some clusters provide a knowledge base for several others. For example, "undergoing cardiac surgery" builds on "acute heart failure", and the "acute heart failure" clustering theme develops into the "undergoing cardiac surgery" clustering theme.

Table 5 listed the top 10 most cited articles, most of which were published in the *Circulation* and *JAMA-Journal of the American Medical Association*. Of these, the article entitled Efficacy and safety of intravenous LEVO compared with dobutamine in severe low-output heart failure (the LIDO study): a randomized double-blind trial was the most frequently cited (n = 431) and was published in 2002 by Follath, F et al. [27]. The remaining nine articles were published in the period of 1994–2007, with the number of citations ranging from 145 to 243.

Of these 10 studies, the top 2 co-cited reference explored the efficacy and safety of LEVO. Among them, RUSSLAN, which was performed by Moiseyev, VS et al. demonstrated LEVO decreased the incidence of worsening heart failure and reduced both short and longer-term mortality [28]. The remaining researches focused on hemodynamic effect of LEVO and the target protein called cardiac troponin C.

3.7. Emerging trends

An article with a high citation burst indicated that it had received significant attention from scientific peers and represented an emerging trend or topic in the research field.

Herein, we determined the top 25 references with the strongest strength citation bursts from 1990 to 2023 in LEVO-related field based on the Citespace software.

The analysis showed that the burst strength of these papers ranged from 18.65 to 62.24, and the burst duration ranged from 3 to 5 years (Fig. 11). Of these papers, the first-ranked paper was published in 2002 and had a burst strength of 62.24 with 4 years of burst duration. This study demonstrated that LEVO could be a better choice than dobutamine as inotropic therapy for patients with decompensated heart failure [27].

The burst of the second-ranked paper was maintained for 4 years (2003–2007), and this study demonstrated that LEVO offers a promising therapeutic option for the management of left ventricular failure complicating an acute myocardial infarction [28]. As for the third-ranked article, its burst strength was 39.63 and lasted from 2008 to 2012. SURVIVE was a randomized trial, which was comparing LEVO with dobutamine in patients with decompensated heart failure to show a difference between the two drugs on mortality at day 180[29].

In conclusion, exploring the security and effectiveness of LEVO and the best use strategies are the main hot spots and trends in the LEVO field at the moment and even for some time to come. Based on the relationship between keywords and the mapping of the subjects of existing literature, the main hotspots including heart failure, cardiac

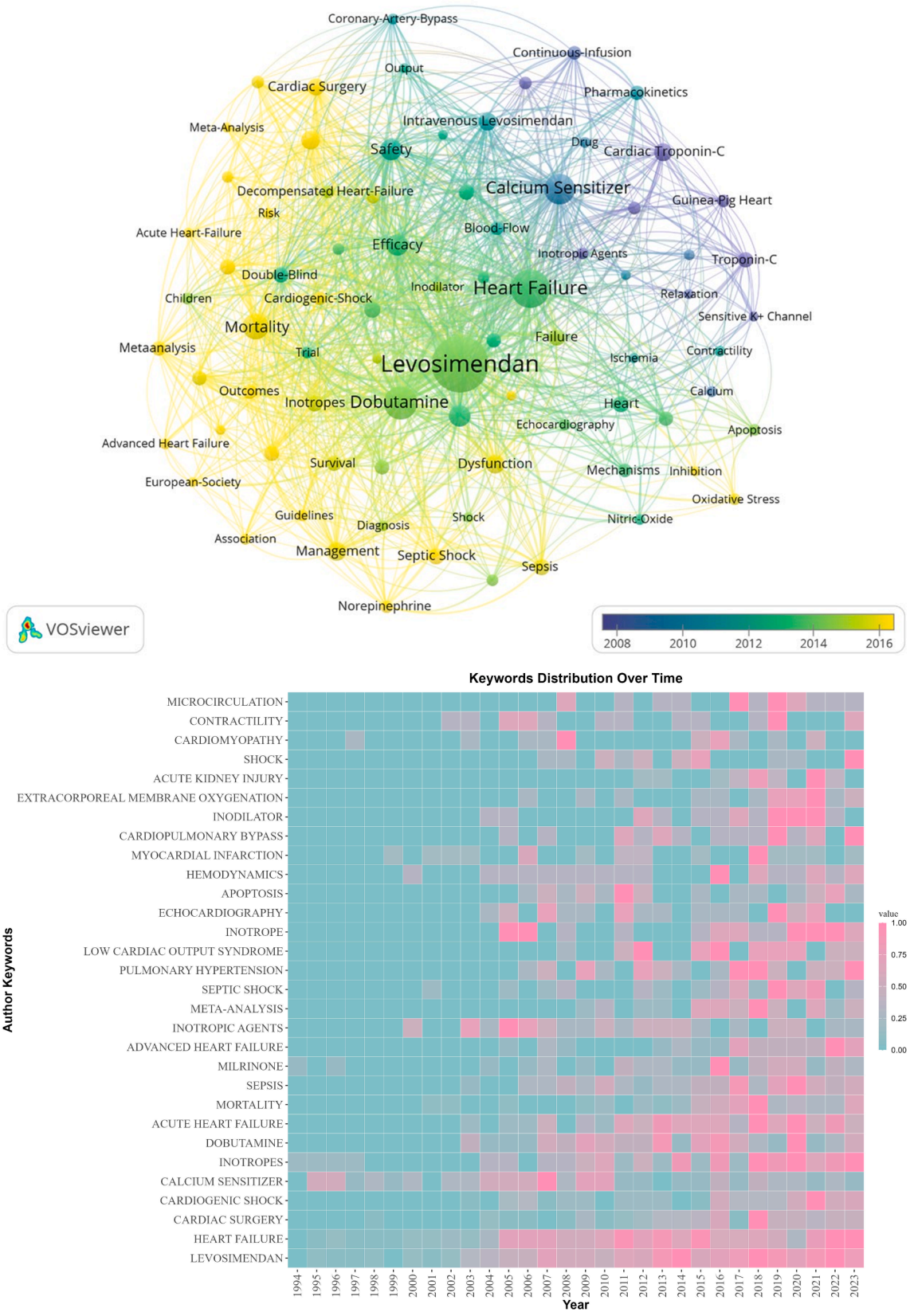

Fig. 8. (*continued*).

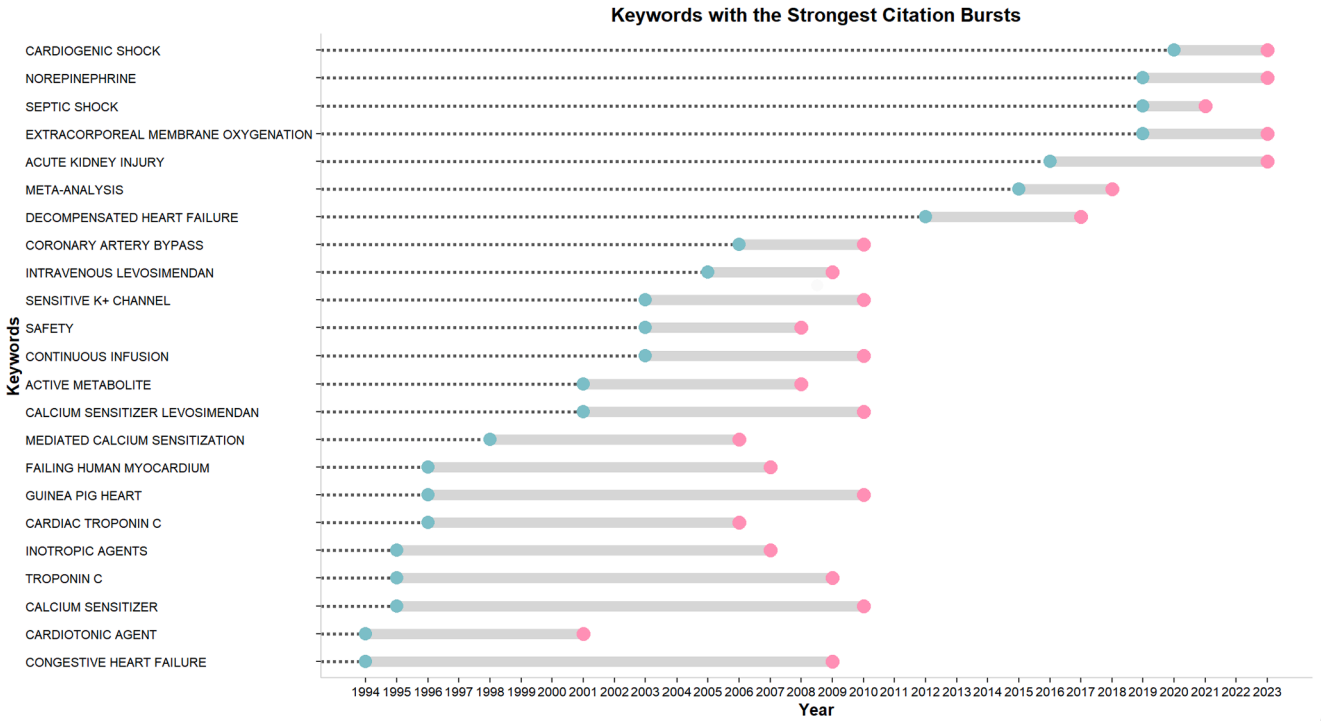

Fig. 8. (*continued*).

surgery, mortality and organ protection indicate the research on the clinical evidence of LEVO reducing mortality in patients undergoing cardiac surgery, the research on the effective strategy of LEVO treatment in patients with heart failure, and the research on the scientific research of LEVO organ protection will be the main research aspects in the future.

4. Discussion

Bibliometric analysis, first used by Alan Pritchard in 1969 [21], a systematic analysis of publications assessing research status and trends, which carries out retrospective reviews, looks for data correlations, makes predictions about future development, and so on [22], is thus used here to provide ideas and directions for future research. Bibliometric and visual analysis can efficiently support information integration to improve the understanding of the research activity.

A bibliometric analysis was performed on 1,432 articles from the WoSCC database from 1990 to 2023 using multiple literature analysis software and computational algorithm. This work summarized research topics, trends, and sources for LEVO as well as obtained an outline of global research on its impact.

From January 1st 1990 to December 31st 2023, it was appeared the first related article for LEVO in 1994 and the annual publications kept a general upward trend, indicating its rapid development and sustained research interest. The publication rate of LEVO experienced a sudden and significant increase in 1994, which can be attributed to the discovery and understanding of the mechanisms of action of LEVO [30]. In 2000, the publications of LEVO increased fastly, which was highly associated with the first approval by Swedish regulatory authorities in 2000 for expanding treatment options for patients with acute heart failure (AHF) or acutely decompensated heart failure (ADHF) [2].

In 2002, LIDO revealed that LEVO could be a better choice than dobutamine as inotropic therapy for patients with decompensated heart failure [27]. In 2002, RUSSLAN, a randomized trial, showed that LEVO offers a promising therapeutic option for the management of left ventricular failure complicating an acute myocardial infarction [28]. These continued to strongly drive the annual output.

The repurposing of LEVO in patients with left ventricular dysfunction undergoing cardiac surgery [31], LEVO for hemodynamic support after cardiac surgery [32], and 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [33] further promoted the development of this field in next few years.

As for the country, the United States is the absolute leader who has the most publications and the highest academic reputation overall. It was worth mentioning that University of Helsinkin and Orion pharma, the top two influential institutions, are from Finland. IV LEVO (SIMDAX®) emerged from a research and development program by Orion Pharma (Espoo, Finland).

At the same time, professor Pollesello, Piero, research scientist and teacher at the Universities of Trieste (Italy) and Helsinki (Finland), senior lecturer (Adjunct Professor, Medical Chemistry), currently at Orion Pharma Critical Care, was the most influential researcher in LEVO filed. Many European countries (the United Kingdom, Germany, Italy, and France) had a relatively large contributions to output.

In terms of scientific collaboration, Italy, Germany and Finland had the most corporations;

Institute-wise, University of Helsinkin, Orion pharma had the most

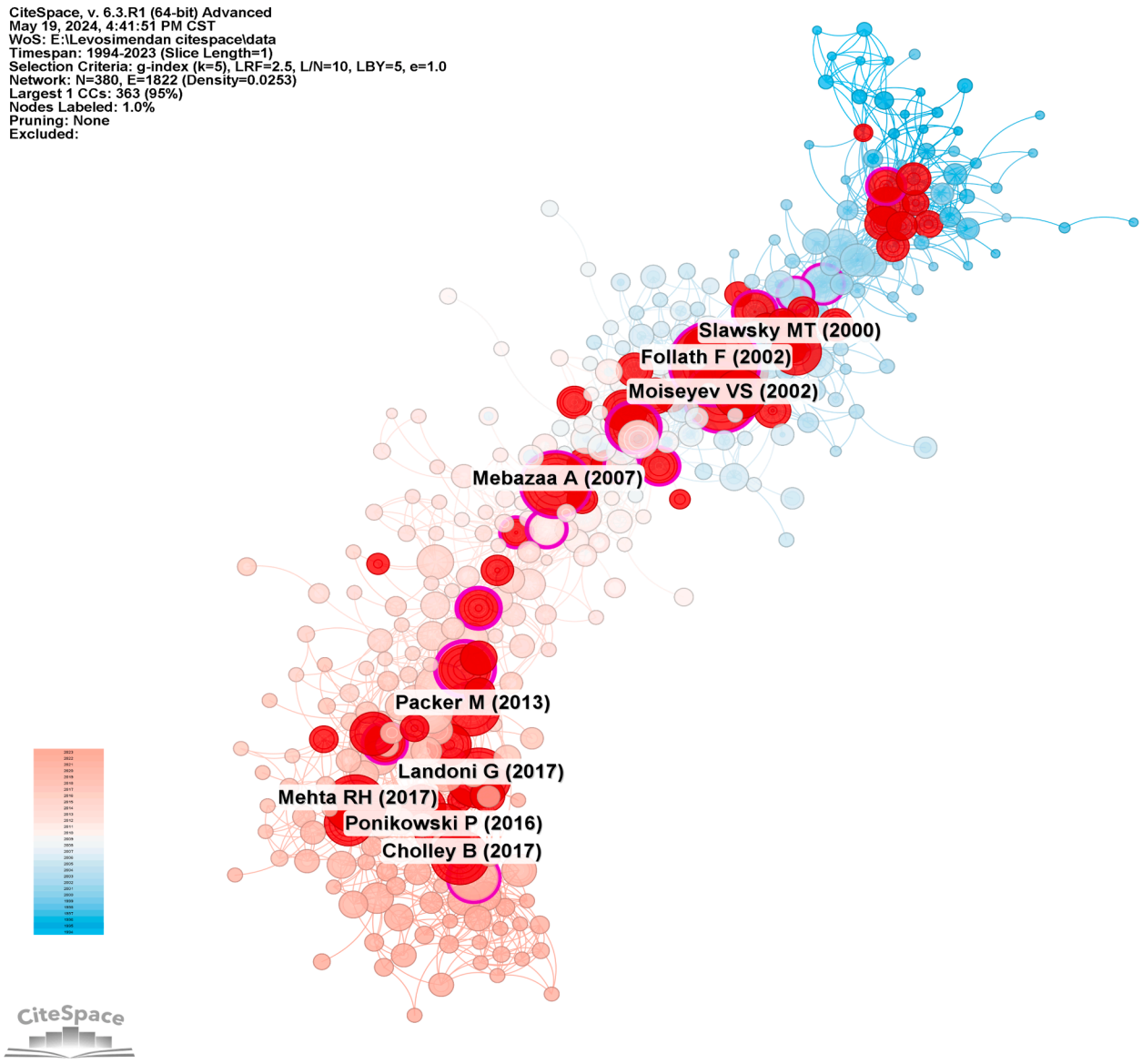

Fig. 9. Co-cited reference analysis. (A) Visualization map of co-cited references; (B) Timeline of co-cited references.

corporations; Author-wise, professor Pollesello,Piero appears to have the widest collaborative network. Professor Pollesello,Piero, and Parissis,John T, and Kivikko,Matti had an active collaboration, which maximized the regional advantages and further strengthening their academic impact.

At the end of this study, we explored the hot spots and trends of LEVO research. As we all know, the strength of a paper's citation burst represents the degree of concern by peers.

This study found that the top 25 references with the strongest strength citation intensity focused on exploring the safety and efficacy of LEVO and the best strategies for its use. Hence, the effectiveness and safety of LEVO and the best strategies for using are the current research hot spot and trend in this field.

In the majority of initial studies, there were most positive outcomes observed, indicating enhancements in hemodynamics and/or organ function, and even implying a decreased mortality rate [27,28,34,35]. In 2007, SURVIVE is a large international multicenter randomized controlled trial (RCT), comparing LEVO with dobutamine in patients with decompensated heart failure failed to show a difference between the two drugs on mortality at day 180[29]. In 2008, PERSIST demonstrated that an experimental end-point, the Patient Journey, did not show differences between oral LEVO and placebo in patients with severe

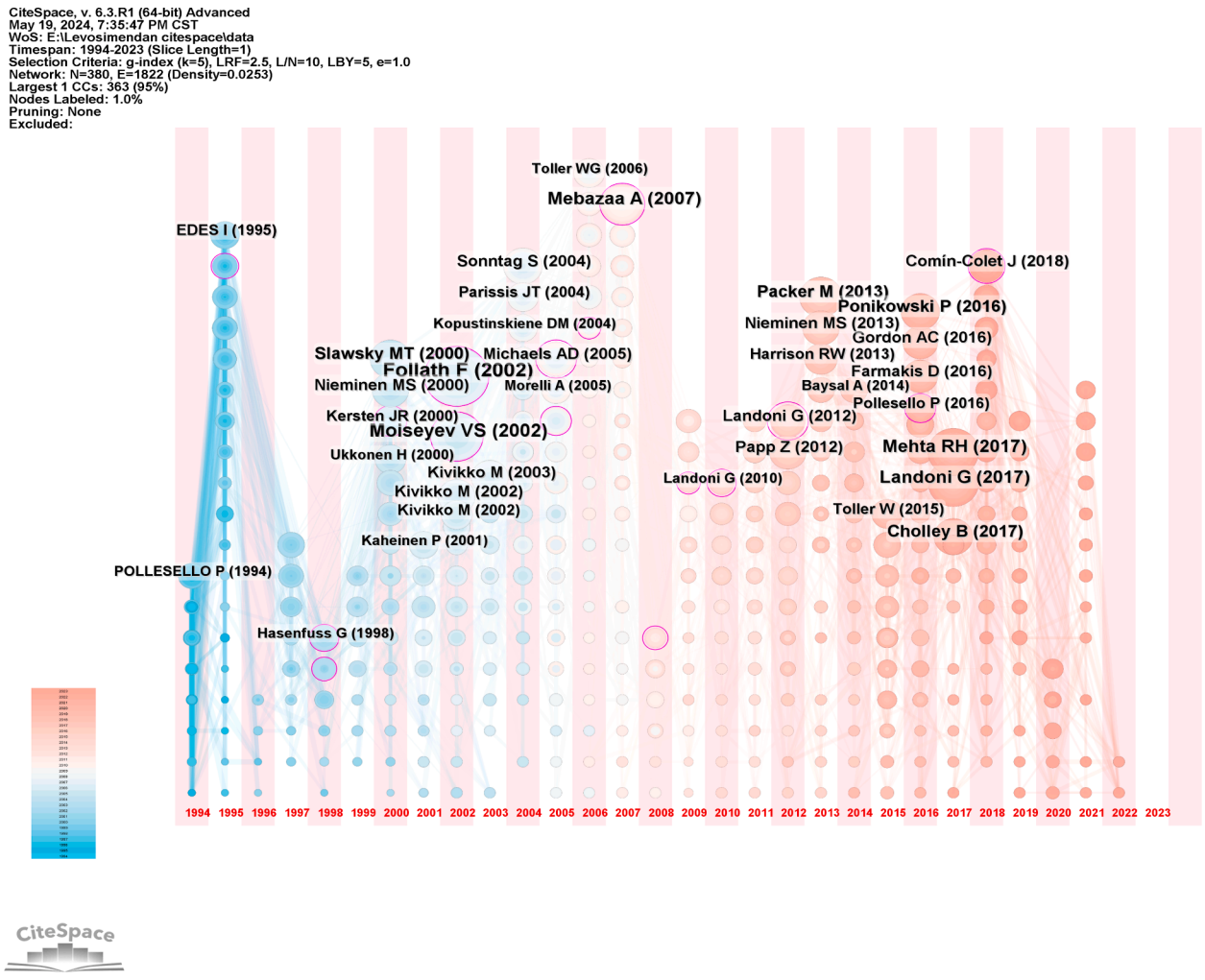

Fig. 9. (*continued*).

CHF [36].

But in 2017, two randomized controlled trials comparing LEVO with placebo on top of standard care in cardiac surgical patients failed to reach statistical significance. One is LEVO CTS, a randomized trial, which addresses the question of the effectiveness of LEVO and showed that prophylactic LEVO did not result in a rate of the short-term composite end point of death, renal-replacement therapy, perioperative myocardial infarction, or use of a mechanical cardiac assist device that was lower than the rate with placebo[31].The other one is CHEETAH, a randomized trial, focused on the role of reducing mortality, demonstrated that low-dose LEVO in addition to standard care did not result in lower 30-day mortality than placebo in patients who required perioperative hemodynamic support after cardiac surgery [32].

The current controversy on this topic of the effectiveness of LEVO is clinically important and is attracting the attention of an increasing number of researchers. In summary, the effectiveness and safety of LEVO and the best strategies for using LEVO are the current research hotspot and trend in this field. Based on the analysis of co-cited references, keyword clusters and keyword bursts, heart failure, cardiac surgery, mortality and organ protection were the main four hotspots. And their main topics had been clearly specified. Clinical evidence of LEVO for reducing mortality in patients undergoing cardiac surgery, effective strategy for the treatment of LEVO in patients with heart failure, and scientific research on the organ protection of LEVO were the main topics in the LEVO filed.

This study also had many limitations. First, the data of the current study were extracted via software tools, which had the potential bias. Second, only data from WoSCC were included in this study, although WoSCC is the most widely and commonly used database for scientometric studies.

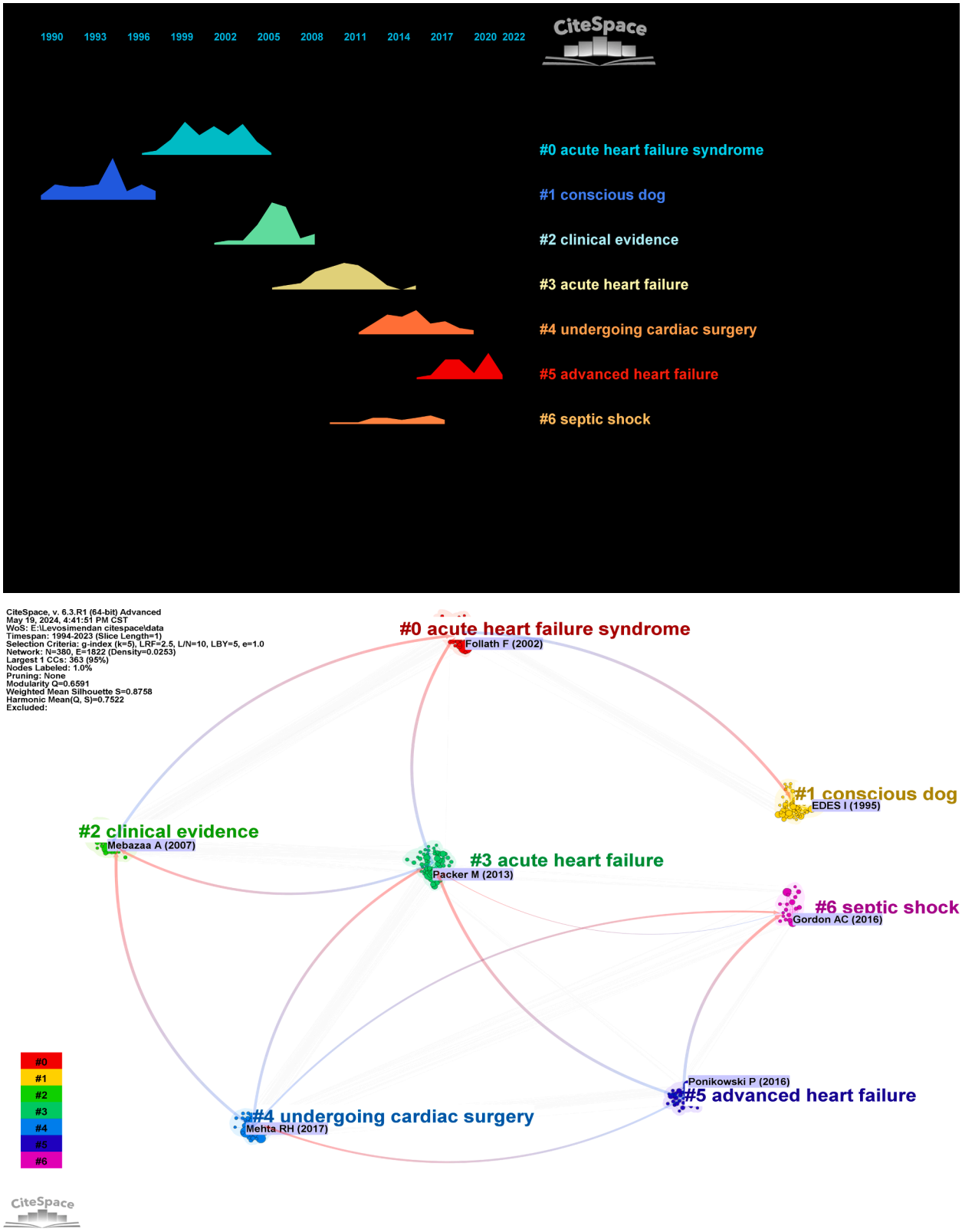

Fig. 10. Cluster analysis of LEVO field. (A) Visualization map of co-cited reference cluster; (B) Evolution of co-cited reference cluster.

5. Conclusions

Currently, LEVO is receiving more and more attention. By utilizing bibliometric analysis and information visualization, it is possible to ascertain the general research patterns and areas in this field, and offer essential information to new researchers. Our research identified countries, institutions, authors, and journals that made noteworthy contributions to LEVO field, as well as the limitations and deficiencies. Moreover, this study confirmed that the safety and efficacy of LEVO, along with the optimal approach for its utilization, are prominent

Table 5
Top 10 co-cited references in the field of LEVO.

Rank	Author	Citations	Title	Journal	Year
1	Follath, F	431	Efficacy and safety of intravenous LEVO compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial	Lancet	2002
2	Moiseyev, VS	243	Safety and efficacy of a novel calcium sensitizer, LEVO, in patients with left ventricular failure due to an acute myocardial infarction-A randomized, placebo-controlled, double-blind study (RUSSLAN)	European Heart Journal	2002
3	Mebazaa,A	227	LEVO vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial	JAMA-Journal of the American Medical Association	2007
4	Slawsky, MT	217	Acute hemodynamic and clinical effects of LEVO in patients with severe heart failure	Circulation	2000
5	Haikala, H	203	Cardiac troponin C as a target protein for a novel calcium sensitizing drug, LEVO	Journal of Molecular and Cellular Cardiology	1995
6	Yokoshiki, H	190	LEVO, a novel Ca2 + sensitizer, activates the glibenclamide-sensitive K + channel in rat arterial myocytes	European Journal of Pharmacology	1997
7	Nieminen, MS	185	Hemodynamic and neurohumoral effects of continuous infusion of LEVO in patients with congestive heart failure	JAMA-Journal of the American Medical Association	2000
8	Pollesello, P	163	Binding of a new Ca2 + sensitizer, LEVO, to recombinant human cardiac troponin C. A molecular modelling, fluorescence probe, and proton nuclear magnetic resonance study	Journal of Biological Chemistry	1994
9	Hasenfuss G	154	Influence of the novel inotropic agent LEVO on isometric tension and calcium cycling in failing human myocardium	Circulation	1998
10	Edes I	145	Effects of LEVO, a cardiotonic agent targeted to troponin C, on cardiac function and on phosphorylation and Ca2 + sensitivity of cardiac myofibrils and sarcoplasmic reticulum in guinea pig heart	Circulation Research	1995

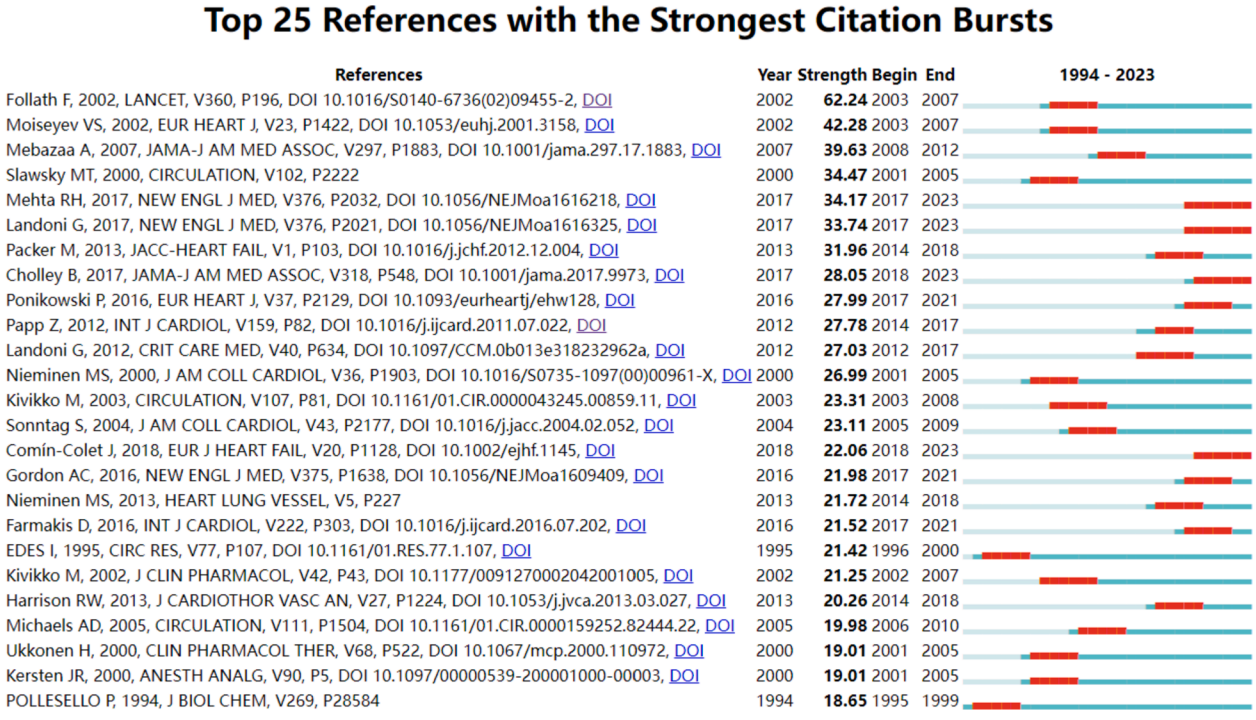

Fig. 11. The top 25 references with the strongest strength citation bursts.

research trends and significant points in this field, both presently and in the future.

CRediT authorship contribution statement

Xian-Shu Zhao: Software, Resources, Methodology. **Yi-Ping Yu:** Project administration, Methodology, Conceptualization. **Yun-Tai Yao:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101571.

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