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Research article

Trends in gut-heart axis and heart failure research (1993–2023): A bibliometric and visual analysis

Jiahui Ouyang [a,b,1], Lingli Zhao [a,b,1], Yewen Song [a], Hua Qu [a,b], Tianyi Du [a,b,c], Liu Shi [a,b,c], Zhijie Cui [a,b], Zhonghui Jiang [a,b,**], Zhuye Gao [a,b,*]

[a] *Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, 100091, China*
[b] *National Clinical Research Center for Chinese Medicine Cardiology, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, 100091, China*
[c] *Graduate School, Beijing University of Chinese Medicine, Beijing, 100029, China*

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ABSTRACT

Background: The incidence of heart failure, the terminal stage of several cardiovascular diseases, is increasing owing to population growth and aging. Bidirectional crosstalk between the gut and heart plays a significant role in heart failure. This study aimed to analyze the gut-heart axis and heart failure from a bibliometric perspective.

Methods: We extracted literature regarding the gut-heart axis and heart failure from the Web of Science Core Collection database (January 1, 1993, to June 30, 2023) and conducted bibliometric and visualization analyses using Microsoft Excel, CiteSpace, VOSviewer, and the R package "bibliometrix."

Results: The final analysis included 1646 articles with an average of 35.38 citations per article. Despite some fluctuations, the number of articles published per year has steadily increased over the past 31 years, particularly since 2018. A total of 9412 authors from 2287 institutions in 86 countries have contributed to this field. The USA and China have been the most productive countries, with the Cleveland Clinic in the USA and Charité-Universitätsmedizin Berlin in Germany being the most active institutions. The cooperation between countries/regions and institutions was relatively close. Professor Tang WHW was the most productive author in the field and the journal *Shocks* published the highest number of articles. "Heart failure," "gut microbiota," "trimethylamine N-oxide," and "inflammation" were the most common keywords, representing the current research hotspots. The keyword burst analysis indicated that "gut microbiota" and "short-chain fatty acids" are the current frontier research topics in this field.

Conclusion: Research on the gut-heart axis and heart failure is increasing. This bibliometric analysis indicated that the mechanisms associated with the gut-heart axis and heart failure, particularly the gut microbiota, trimethylamine N-oxide, inflammation, and short-chain fatty acids, will become hotspots and emerging trends in research in this field. These findings provide valuable insights into current research and future directions.

* Corresponding authorXiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, 100091, China.
** Corresponding authorXiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, 100091, China.
E-mail addresses: jzh2021@126.com (Z. Jiang), zhuyegao@126.com (Z. Gao).
[1] Jiahui Ouyang and Lingli Zhao are co-first authors.

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1. Introduction

Heart failure (HF) is a multifaceted chronic and progressive condition in which the myocardium fails to pump sufficient blood to fulfill the body's demands for oxygen and nutrients; it represents the terminal stage of many cardiovascular diseases (CVDs) [1]. The global incidence of HF exceeds 64 million individuals [2,3], and this number is expected to increase owing to population growth, aging populations, and increased survival rates following diagnosis [4]. This large and increasing healthcare burden poses significant societal challenges [4].

The gut microbiota (GM), which consists of trillions of bacteria in the gastrointestinal tract, plays essential roles in the regulation of host immunity and maintenance of metabolic homeostasis [5] and is closely associated with human health [6]. Dysbiosis, characterized by imbalances in the composition and function of the GM, has been implicated in the pathogenesis and progression of a broad range of conditions, including gastrointestinal, inflammatory, and metabolic diseases, and CVDs [7]. Growing evidence indicates a correlation between the GM and HF [8]. This correlation refers to bidirectional crosstalk between the heart, gut, and GM known as the "gut-heart axis" [9]. In HF, this primarily refers to the hemodynamic changes caused by HF, including reduced perfusion and tissue hypoxia, triggering intestinal mucosal barrier dysfunction, leading to increased intestinal permeability. Consequently, bacteria, endotoxins, and metabolic byproducts translocate from the gut into the systemic circulation, triggering systemic inflammation [10]. Furthermore, HF is associated with GM dysbiosis and potentially the abnormal production of gut microbe-derived metabolites [9]. This imbalance in gut microbe-derived metabolites combined with gut epithelial dysfunction contributes to cardiac dysfunction, inflammation, malnutrition, and other health issues in patients with HF [9]. Owing to these effects, GM profiles may serve as potential biomarkers in patients with HF [11].

Current research in this field relies heavily on manual searches and personal experience, which lack a comprehensive and holistic approach. Bibliometrics, a literature analysis method that employs mathematical and statistical techniques, provides quantitative and qualitative evaluations of publications within a specific research field [12]. This method compares contributions from different countries/regions, institutions, authors, journals, references, and keywords, thereby identifying scientific output, research hotspots, and developing trends within a particular field [13].

In recent years, extensive research has been conducted on the gut-heart axis and HF [14–17], suggesting innovative diagnostic and therapeutic approaches for HF [9,18]. A thorough understanding of the current research trends in this field is therefore crucial. This study presents a comprehensive exploration of the gut-heart axis in HF research from a bibliometric perspective, offering insights into the current state, future development trends, and prospects in this field.

2. Materials and methods

2.1. Data sources and search strategy

This bibliometric and visual analysis was based on a comprehensive search of the Science Citation Index Expanded and Social

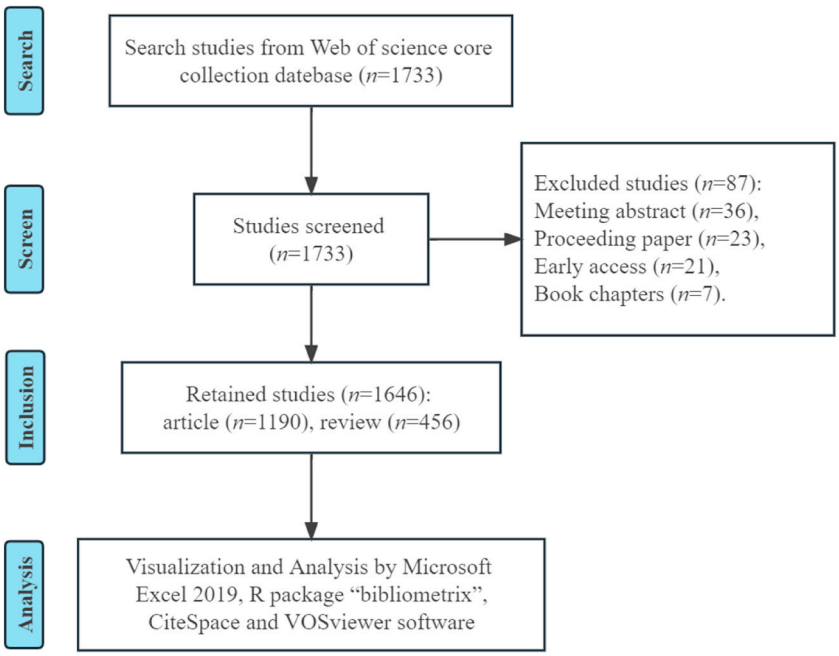


Fig. 1. Flowchart of the literature screening process.

Sciences Citation Index databases in the Web of Science Core Collection (WoSCC) database (https://www.webofscience.com/wos/woscc/basic-search), which are the most widely used and suitable sources for bibliometric analyses [19,20], for publications related to the gut-heart axis and HF published from January 1, 1993, to June 30, 2023. Only publications defined as "articles" or "reviews" were included in the analysis; other publications such as meeting abstracts, proceedings papers, or book chapter were excluded. Publications that had not been formally published, such as early access papers, were also excluded.

In accordance with previous studies [12], we used the key terms recommended previously for the gut-heart axis and HF, such as "microbiome," "gut," "gut-heart axis," and "heart failure" as search terms. The detailed search terms were set as follows: [TS = (microbiome OR microbiota OR flora OR intestinal OR dysbiosis)] AND [TS = (gut OR gastrointestinal OR intestinal OR gut-heart axis OR heart-gut axis)] AND [TS = (heart failure OR cardiac failure)] AND [LA = (English)]. The type of publication was set to "articles" and "reviews." Bibliometric data was exported as "plain text file" documents with the record content set to "Full Record and Cited References."

A total of 1733 records were retrieved; 87 publications were excluded due to document type or non-publication, including 36 conference abstracts, 23 proceedings papers, 21 early access papers, and 7 book chapters. Ultimately, 1646 retrieved records were analyzed. The detailed literature screening process is shown in Fig. 1.

2.2. Data analysis

Information from each publication, including publication year, total number of citations, country/region, institution, journal, journal impact factor (IF), authors, references, and keywords, were extracted from the WoSCC database. Microsoft Office Excel 2019, the "bibliometrix" package in R software [21], VOSviewer software version 1.6.18 [22], and CiteSpace software version 6.2. R2 [23] were used for the bibliometric and visual analyses.

Microsoft Office Excel 2019 was used to visualize the annual number of publications (NP) and number of citations (NC). A global distribution network of publications on the gut-heart axis and HF was constructed in the R package "bibliometrix" (https://www.bibliometrix.org).

VOSviewer software is widely used for bibliometric analysis and scientific mapping. It allows the visualization of collaborative relationships, co-occurrences between countries/regions, institutions, journals, co-cited journals, authors, and co-cited authors, as well as research topics in the field of the gut-heart axis and HF. A node on a map represents a country/region, institution, journal, author, or keyword and its size is positively correlated with the NP or keyword occurrences. The line thickness between nodes indicates the strength of associations, with broader lines indicating tighter cooperation; this can also be described in terms of total link strength (TLS). Different colors in the network visualization represent different clusters. In the overlay visualization, the colors are sorted from blue to yellow by the average publication year (APY).

CiteSpace is another bibliometric analysis and visualization software, developed by Professor Chaomei Chen. In our study, CiteSpace software was used to perform citation burst analysis of references and keywords. The intensity value reflects the cited frequency, and the red bar displays the years of burst.

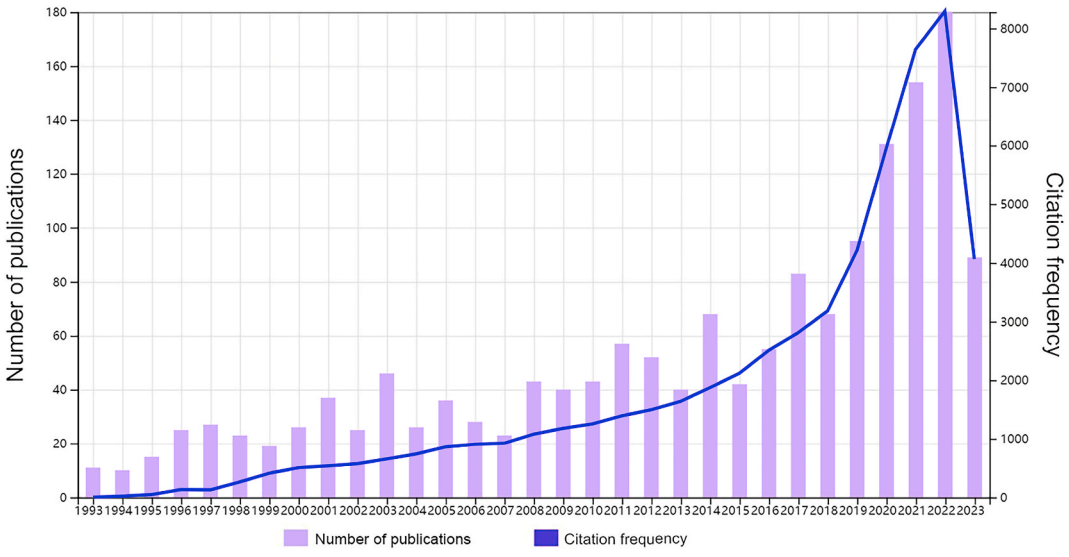


Fig. 2. Temporal distribution map of publications and citations. The number of annual publications and citations for the period from 1993 to 2023 are presented.

3. Results

3.1. Publication outputs and temporal trends

Annual publications provide an overview of developments in a particular field. From January 1993 to June 2023, a total of 1646 studies were published, including 1190 "articles" and 456 "reviews." These studies received 58234 citations, with an average of 35.38 citations per study. Fig. 2 displays the general upward trend in publications on the gut-heart axis and HF; annual publications showed a fluctuating increase until 2018, followed by a rapid increase. Fig. 2 also indicates an increasing trend in citation frequency on the gut-heart axis and HF, again particularly since 2018. This demonstrates the growing number of scholars conducting research in this field.

3.2. Country/region and institutional analysis

The 1646 publications originated from 2287 institutions across 86 countries/regions. The ten most productive countries/regions and institutions are listed in Table 1. The USA (NP: 511, 31.04%) and China (NP: 264, 16.04%) were the most productive countries, with the combined number of publications from the USA and China accounting for almost half of the total (47.08%), indicating their research strength and influence in the field of gut-heart axis and HF-related research. These countries were followed by Germany (NP: 141, 8.57%), Italy (NP = 122, 7.41%), Japan (NP: 111, 6.74%), and England (NP: 110, 6.68%).

We used VOSviewer software to filter the 43 countries/regions with five or more publications and construct collaborative networks based on the number of publications and relationships within each country/region (Fig. 3A). Each circle in Fig. 3A represents a country/region; the circle size is proportional to the number of publications, and the circle color represents the APY. Fig. 3A reveals that the USA is the primary core country in this research field with the highest NP, and China has the highest APY (2020.00), indicating that although China entered this field relatively late, it has rapidly caught up in recent years. Additionally, we utilized the R package "bibliometrix" to create a geographic visualization of the international cooperation map for each country/region (Fig. 3B). The darker the blue color filling the country/region, the higher the number of publications. The line thickness between countries/regions indicates the strength of international collaborative relationships, with broader lines representing stronger cooperation. Fig. 3B reveals that the closest cooperation existsbetween the USA and China, and active cooperation between the USA, Germany, and England is also apparent.

The ten most productive institutions are listed in Table 2. The most prolific organizations were the Cleveland Clinic (NP: 34, 2.07%), followed by Charité-Universitätsmedizin Berlin (NP: 30, 1.829%), the University of Pittsburgh (NP: 23, 1.40%), and Harvard University (NP: 22, 1.34%). Almost all of the top ten institutions were in the USA, indicating the dominance of the USA in the field of the gut-heart axis and HF.

Supplementary Fig. 1 illustrates collaborations between 158 institutions with at least 5 publications each. Charité-Universitätsmedizin Berlin (TLS: 62) in Germany and the Cleveland Clinic (TLS: 42) in the USA have the strongest collaborations with other institutions. Supplementary Fig. 1A highlights the strong collaboration between institutions such as Oslo University Hospital (Oslo, Norway) and Oslo University (Oslo, Norway), and Baker IDI Heart and Diabetes Institute (Melbourne, Australia) and Monash University (Melbourne, Australia). Supplementary Fig. 1B shows the recent active involvement of Chinese institutions in gut-heart axis and HF research (highlighted in yellow), such as Southern Medical University (NP: 10, APY: 2022.00), Zhejiang University (NP: 6, APY: 2022.00), and Chinese Academy of Medical Sciences & Peking Union Medical College (NP: 7, APY: 2021.71).

3.3. Authors and Co-cited authors

A total of 9412 authors were associated with gut-heart axis and HF research publications. Table 3 lists the ten authors with the highest number of publications and citations. Tang WHW of the Cleveland Clinic Heart and Vascular Institute had the most publications (NP: 21, NC: 3584), followed by Hazen SL (NP: 17, NC: 3425), Anker SD (NP: 15, NC: 1508), and Wang Z (NP: 10, NC: 1511). In addition, we observed close cooperation among several authors. For example, Hazen SL closely collaborated with Tang WHW and Wang Z, while Anker SD actively collaborated with Von Haehling S and Sandek A (Fig. 4A).

Table 1
Publications in the 10 most productive countries/regions.

Rank	Country/Region	NP	Proportion	NC	TLS
1	USA	511	31.04%	27295	261
2	China	264	16.04%	6744	80
3	Germany	141	8.57%	6116	180
4	Italy	122	7.41%	3729	130
5	Japan	111	6.74%	2115	130
6	England	110	6.68%	6570	183
7	France	65	3.95%	2133	110
8	Netherlands	61	3.71%	2101	103
9	Canada	56	3.40%	2813	17
10	Australia	50	3.04%	2407	44

NP: Number of publications; NC: Number of citations; TLS: Total link strength.

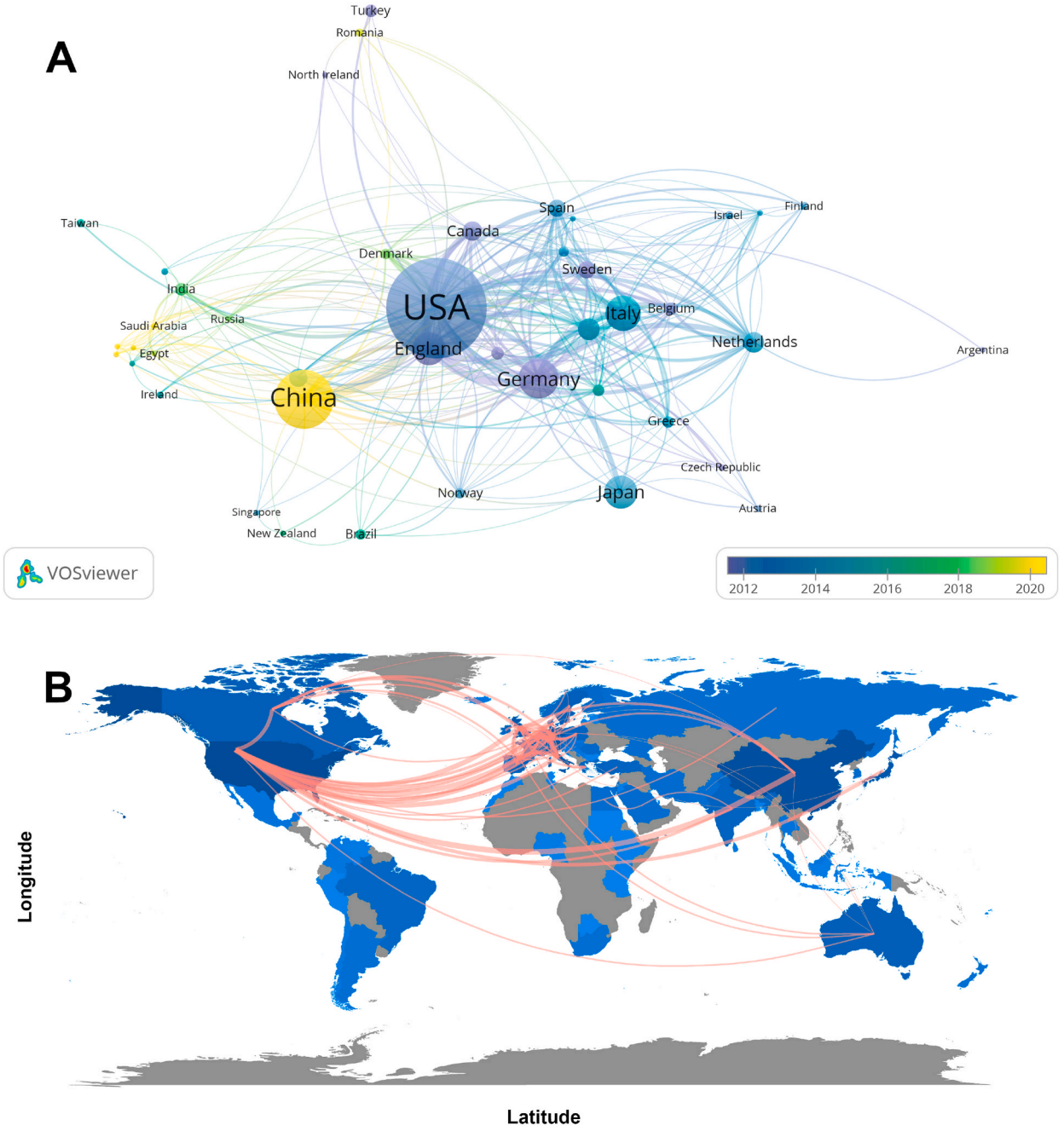


Fig. 3. Visualization of countries/regions involved in gut-heart axis and heart failure research. (A) Collaborative network visualization of countries/regions. (B) Geographic distribution and collaboration map of countries/regions.

Co-cited authors refer to two or more authors who are cited simultaneously in a study, indicating similarities in their research. The analysis of these authors can reveal highly influential experts in a subject area. A total of 57369 co-cited authors were identified. Three experts were co-cited more than 300 times: Tang WHW (NC: 693), Wang Z (NC: 364), and Sandek A (NC: 322) (Table 3). VOSviewer software was used to construct a collaborative network with a minimum co-citation threshold of 50 (Fig. 4B). Circles belonging to a cluster have the same color, and the five colors indicate that these authors belong to five research groups with similar interests.

3.4. Journals and Co-cited journals

Publications on the gut-heart axis and HF were published in 761 journals, of which 65 published more than 5 articles. *Shocks*

Table 2
Publications in the 10 most productive institutions.

Rank	Institution	Country	NP	Proportion	NC	TLS
1	Cleveland Clinic	USA	34	2.07%	4608	42
2	Charité-Universitätsmedizin Berlin	Germany	30	1.82%	1687	62
3	University of Pittsburgh	USA	23	1.40%	1964	30
4	Harvard University	USA	22	1.34%	2359	26
5	University of California, San Diego	USA	15	0.91%	839	16
6	University of Copenhagen	Denmark	15	0.91%	468	32
7	Oslo University	Norway	14	0.85%	686	29
8	Columbia University	USA	14	0.85%	310	11
9	University of California, Los Angeles	USA	13	0.79%	1224	19
10	Stanford University	USA	13	0.79%	1021	26

NP: Number of publications; NC: Number of citations; TLS: Total link strength.

Table 3
Top 10 authors and co-cited authors related to the gut-heart axis and heart failure.

Rank	Authors	NP	NC	Cited Authors	NC
1	Tang WHW	21	3584	Tang WHW	721
2	Hazen SL	17	3425	Wang Z	383
3	Anker SD	15	1508	Sandek A	341
4	Wang Z	10	1511	Koeth RA	203
5	von Haehling S	8	1034	Marques FZ	156
6	Troseid M	8	337	Anker SD	145
7	Pierro A	8	242	Pasini E	129
8	Sandek A	7	1016	Zhu W	128
9	Marques FZ	7	697	Troseid M	123
10	Li l	7	583	Deitch EA	122

NP: Number of publications; NC: Number of citations.

published the most articles (NC: 23), followed by *Journal of Surgical Research* (NC: 21), *Frontiers in Cardiovascular Medicine* (NC: 21), and *Critical Care Medicine* (NC: 20) (Table 4). However, the ranking of journals based on the number of citations was inconsistent with the ranking based on the number of publications (Table 4). As an influential journal, *Circulation Research* had the highest number of citations, with 2931 citations of only 14 publications. This was followed by *Critical Care Medicine* with 1095 citations of 20 publications. The ten journals with the highest number of publications were all in Q1 or Q2 according to Journal Citation Reports (JCR); nine had IFs above 3.

Regarding co-cited journals, 188 of the 8099 journals were cited over 100 times, and eight had citations surpassing 1000 (Table 4). *Circulation* was the most co-cited journal (NC: 2619), followed by *The New England Journal of Medicine* (NC: 1714), *Journal of the American College of Cardiology* (NC: 1669), and *Nature* (NC: 1660), all with more than 1500 citations. Supplementary Fig. 2 shows that *Circulation* has an active co-citation relationship with other journals.

3.5. Co-cited references and references bursts

Co-cited references are those cited simultaneously in one or more articles, forming the knowledge base of a particular field. The frequent citations of these references indicate their wide relevance and similar research themes. In the context of the gut-heart axis and HF, a total of 80,634 co-cited references were identified. The ten most frequently cited references [24–33], all of which are research articles, are presented in Table 5.

The article "Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease" [24], published in Nature by Wang Z et al., received the highest number of citations. Wang Z et al. conducted metabolomics research and identified, for the first time, a correlation between increased levels of specific metabolites in plasma and an increased risk of CVD [24].

A reference burst refers to the frequent citation of a reference in a particular period of time and reflects a change in the focus of research in a given field over time [34]. Reference bursts were analyzed and visualized using CiteSpace software; the 25 references with the strongest citation bursts are shown in Fig. 5. Each bar represents a year, and the red bars represent the citation bursts occurring between 2009 and 2023. The article "Prognostic Value of Elevated Levels of Intestinal Microbe-Generated Metabolite Trimethylamine-N-Oxide in Patients With Heart Failure: Refining the Gut Hypothesis" [27] by Tang WHW et al., in the *Journal of the American College of Cardiology* demonstrated the strongest citation burst. This study [27], with a strength of 22.55, was the first to verify the association between elevated trimethylamine-N-oxide (TMAO) levels and poor prognosis in patients with HF, therefore significantly advancing understanding of the gut-heart axis and HF. Five of the 25 strongest citation bursts were authored by Tang WHW, demonstrating the influence of this research group.

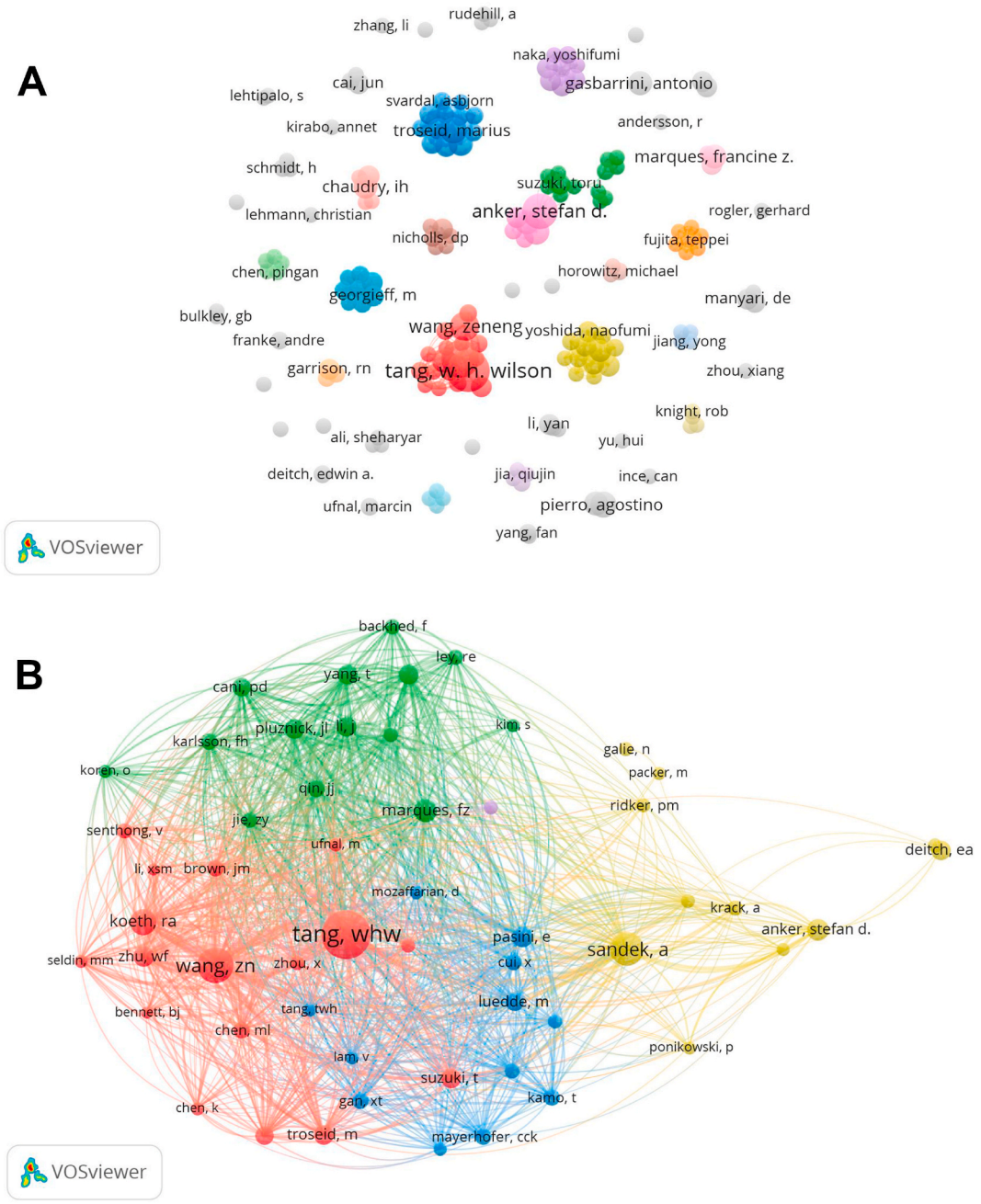


Fig. 4. Visualization of authors involved in gut-heart axis and heart failure research. (A) Collaborative network visualization of authors. (B) Collaborative network visualization of co-cited authors.

3.6. Keyword and keyword bursts

Keyword analysis can identify hotspots and directions in the field. Table 6 lists the 20 most frequently occurring keywords in the field of the gut-heart axis and HF. “Heart failure” was the most important term with 504 occurrences, followed by “gut microbiota” (235 occurrences), “trimethylamine N-oxide” (177 occurrences), “inflammation” (153 occurrences), “cardiovascular disease” (149 occurrences), “myocardial infarction” (115 occurrences), and “metabolism” (106 occurrences).

The 32 keywords with at least 50 occurrences were analyzed using VOSviewer software to identify hot topics and future directions. The analysis resulted in three clusters representing three research directions (Fig. 6A). The blue cluster includes keywords such as “trimethylamine N-oxide,” “metabolism,” risk,” “microbiota,” and “phosphatidylcholine.” The red cluster consists of keywords such as “inflammation,” “myocardial infarction,” “oxidative stress,” and “mortality.” The green cluster includes keywords such as “heart

Table 4
Top 10 journals and co-cited journals related to the gut-heart axis and heart failure.

Rank	Journal	NP	NC	IF (JCR 2022)	JCR Quartile	Co-cited journal	NC	IF (JCR 2022)	JCR Quartile
1	Shock	23	1002	3.1	Q1	Circulation	2619	37.8	Q1
2	Journal of Surgical Research	21	342	2.2	Q2	The New England Journal of medicine	1714	158.5	Q1
3	Frontiers in Cardiovascular Medicine	21	87	3.6	Q2	Journal of the American College of Cardiology	1669	24.0	Q1
4	Critical Care Medicine	20	1095	8.8	Q1	Nature	1660	64.8	Q1
5	International Journal of Molecular Sciences	17	287	5.6	Q1	Circulation Research	1302	20.1	Q1
6	Nutrients	17	245	5.9	Q1	Proceedings of the National Academy of Sciences of the United States of America	1234	11.1	Q1
7	American Journal of Physiology-Heart and Circulatory Physiology	15	330	4.8	Q1	PLoS One	1168	3.7	Q2
8	Circulation Research	14	2931	20.1	Q1	Lancet	1153	168.9	Q1
9	Biomedicines	14	76	4.7	Q1	European Heart Journal	933	7.1	Q1
10	Intensive Care Medicine	12	260	38.9	Q1	Hypertension	930	8.3	Q1

NP: Number of publications; NC: Number of citations; IF: Impact Factor; JCR: Journal Citation Reports.

Table 5
Top 10 co-cited references regarding the gut-heart axis and heart failure.

Rank	Title	First author	Publication year	Journal	NC
1	Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease [24]	Wang Z	2011	Nature	177
2	Altered intestinal function in patients with chronic heart failure [25]	Sandek A	2007	Journal of the American College of Cardiology	149
3	Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis [26]	Koeth RA	2013	Nature Medicine	144
4	Prognostic Value of Elevated Levels of Intestinal Microbe-Generated Metabolite Trimethylamine-N-Oxide in Patients With Heart Failure Refining the Gut Hypothesis [27]	Tang WHW	2014	Journal of the American College of Cardiology	142
5	Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk [28]	Tang WHW	2013	The New England Journal of Medicine	134
6	Pathogenic Gut Flora in Patients With Chronic Heart Failure [29]	Pasini E	2016	JACC. Heart Failure	122
7	High-Fiber Diet and Acetate Supplementation Change the Gut Microbiota and Prevent the Development of Hypertension and Heart Failure in Hypertensive Mice [30]	Marques FZ	2017	Circulation	118
8	Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk [31]	Zhu W	2016	Cell	103
9	Heart failure is associated with depletion of core intestinal microbiota [32]	Luedde M	2017	European Journal of Heart Failure	102
10	Non-lethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis [33]	Wang Z	2015	Cell	97

NC: Number of citations.

failure," "gut microbiota," "cardiovascular disease," "intestinal microbiota," and "hypertension." In the overlay visualization (Fig. 6B), keywords are marked with different colors according to their APY. Keywords highlighted in yellow, such as "short-chain fatty acids," "gut microbiota," and "trimethylamine N-oxide," are those that have become increasingly popular in recent years and may be prospective hot topics.

Furthermore, the analysis of keyword bursts using CiteSpace software revealed that "gut microbiota" and "short-chain fatty acids" had the most recent bursts, suggesting their potential as future research hotspots in the field of the gut-heart axis and HF (Fig. 6C).

4. Discussion

In recent decades, there has been a dramatic increase in the prevalence of HF, which is now a major global health issue. HF is a complex syndrome with different etiologies, of which ischemic heart disease and hypertension are the most common causes [35]. Other specific risk factors include obesity, type 2 diabetes mellitus (T2DM), and valvular heart disease, all of which contribute to the acceleration of cardiovascular aging [36]. These risk factors can act independently or more commonly in combination, either directly or indirectly. Myocardial metabolism is almost exclusively aerobic, and oxygen delivery depends on arterial oxygen content and coronary blood flow. Ischemia irreversibly impairs cardiac function and alters the size and shape of the failing heart, known as ventricular remodeling. In the case of acute ischemia, for example in acute myocardial infarction, the loss of functioning cardiomyocytes leads to myocardial stunning and necrosis, followed by inflammation, hypertrophy, and fibrosis. These changes activate a

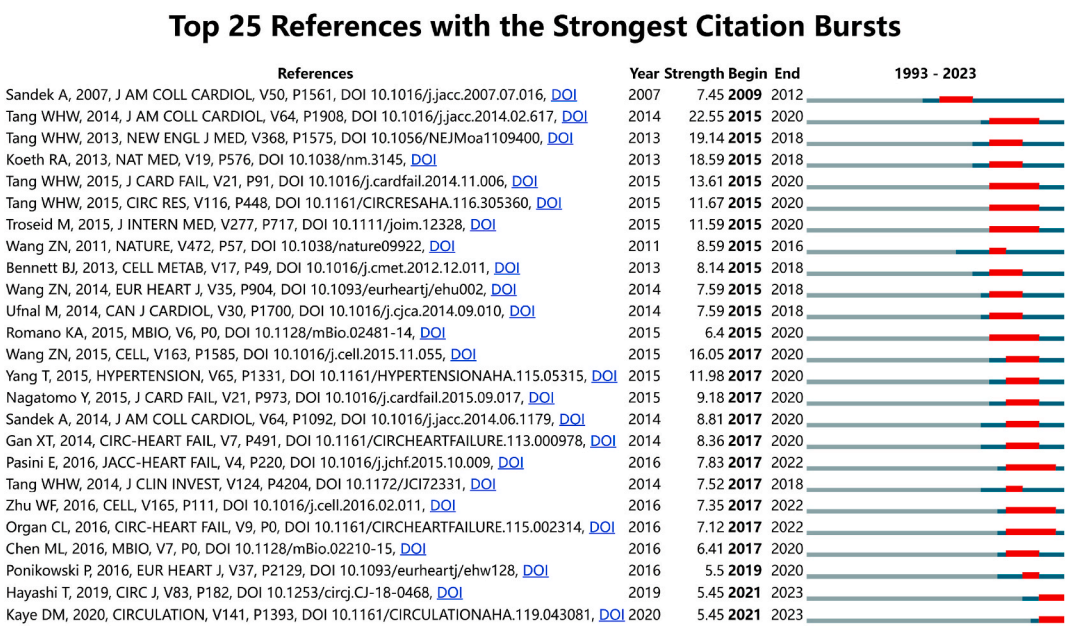


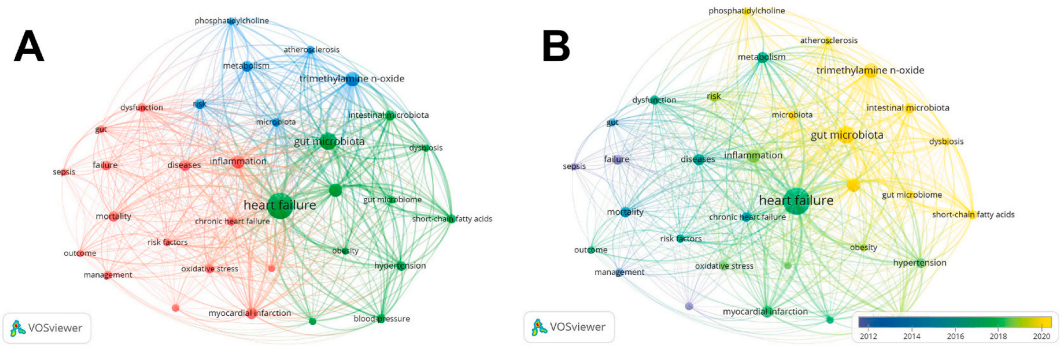
Fig. 5. Top 25 references with the strongest citation bursts from 1993 to 2023. Red bars indicate the length of the bursts. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 6
Top 20 keywords regarding the gut-heart axis and heart failure.

Rank	Keywords	Occurrences	Rank	Keywords	Occurrences
1	heart failure	504	11	risk	93
2	gut microbiota	235	12	failure	84
3	trimethylamine N-oxide	177	13	hypertension	83
4	inflammation	153	14	dysfunction	81
5	cardiovascular disease	149	15	Short-chain fatty acids	79
6	myocardial infarction	115	16	blood pressure	77
7	metabolism	106	17	oxidative stress	74
8	diseases	104	18	chronic heart failure	74
9	intestinal microbiota	97	19	management	67
10	mortality	97	20	microbiota	66

neurohormonal cascade, leading to adverse left ventricular remodeling and subsequent dilation and functional impairment, which is the primary pathophysiological mechanism of HF [37]. Longstanding hypertension causes constant cardiac pressure and overload, and drives left ventricular hypertrophy, myocardial fibrosis, and diastolic dysfunction, resulting in hypertensive heart disease, including left ventricular diastolic dysfunction and dilated cardiomyopathy with HF and reduced ejection fraction, which ultimately manifests as HF [38]. Obesity and T2DM may lead to HF through myocardial infarction and left ventricular remodeling [36]. Cardiotoxicity caused by chemotherapy and other factors can also significantly contribute to the development of HF [39].

In recent years, numerous studies have demonstrated that the GM represents an important component of human physiology and metabolic homeostasis, and can directly or indirectly through derived metabolites, affect the heart and exacerbate the progression of HF [40], making the GM a new and promising therapeutic target for the treatment of HF [41]. One important aspect of this relationship is the metabolic pathways within the GM, including the production of trimethylamine (TMA)/TMAO, short-chain fatty acids (SCFAs), and secondary bile acids (BAs). These are well known pathophysiological linkages between biological processes dysregulated in HF, such as cardiac remodeling and repair capability, systemic vascular and inflammatory tone, and energy metabolism [15,42,43]. TMA, a GM-derived metabolite resulting from diets abundant in phosphatidylcholine, choline, betaine, and L-carnitine [44,45], can be converted into TMAO by hepatic flavin-containing monooxygenase 3 in the liver [46]. Circulating TMAO can activate platelet aggregation, increase foam cell formation, induce inflammatory responses, decrease reverse cholesterol transport, and accelerate endothelial dysfunction, contributing to the progression of atherosclerosis and HF [24,47–50]. Li Z et al. [51] demonstrated that TMAO promotes myocardial hypertrophy and fibrosis through the Smad3 signaling pathway, both in vivo and in vitro. In cardiomyocytes, TMAO decreases energy metabolism and mitochondrial function by affecting pyruvate and fatty acid oxidation, which are involved in the tricarboxylic acid cycle [52]. It also negatively affects myocardial contractile function and intracellular calcium processing [53]. This pathway may be influenced by dietary factors such as foods or nutritional supplements rich in phosphatidylcholine, including red meat, eggs, milk, and certain fish [54], which may increase the risk of CVD through its metabolites, such as choline [24]. Saturated



C **Top 25 Keywords with the Strongest Citation Bursts**

Keywords	Year	Strength	Begin	End	1993 - 2023
multiple organ failure	1993	20.51	1993	2010	
congestive heart failure	1993	17.77	1993	2014	
blood flow	1993	16.3	1993	2008	
tumor necrosis factor	1994	12.19	1994	2010	
failure	1993	12.12	1993	2010	
atrial natriuretic peptide	1993	6.99	1993	2012	
bacterial translocation	1994	6.69	1994	2016	
septic shock	1995	14.72	1995	2012	
vasoactive intestinal peptide	1995	8.37	1995	2014	
hemorrhagic shock	1995	7.05	1995	2002	
cardiopulmonary bypass	1997	14.66	1997	2014	
rat	1997	14.26	1997	2012	
nitric oxide	1997	10.24	1997	2010	
cardiac surgery	1997	9.49	1997	2014	
cardiac output	1997	9.09	1997	2004	
sepsis	1997	8.61	1997	2008	
organ failure	1997	6.5	1997	2000	
nitric oxide synthase	2001	6.74	2001	2012	
intestinal permeability	2001	6.51	2001	2014	
management	2003	7.38	2003	2016	
mortality	2003	9.22	2007	2014	
therapy	2013	6.71	2013	2016	
l carnitine	2015	6.83	2015	2018	
gut microbiota	2015	16.2	2021	2023	
short-chain fatty acids	2017	8.28	2021	2023	

Fig. 6. Analysis of keywords in gut-heart axis and heart failure research. (A) Network visualization of keywords. (B) Overlay visualization of keywords. (C) Top 25 keywords with the strongest citation bursts from 1993 to 2023.

fatty acids with six or fewer carbon molecules are defined as SCFAs, and include cellulose, lignin, and pectin [55]. SCFAs can serve as a source of energy or fuel for glucose and lipid synthesis [56,57], and are also anti-inflammatory, as they bind to signaling receptors on target cells to modulate immune cell chemotaxis and cytokine release [58]. Additionally, SCFAs help reduce blood pressure and accompanying cardiac hypertrophy and myocardial fibrosis [58]. Primary BAs are synthesized in the liver through cholesterol oxidation [59], and secondary BAs, such as deoxycholate, lithocholate, and ursodeoxycholate (UDCA), are derived from primary BAs through a process that relies on the unique biosynthetic capabilities of certain microbes [60]. Early studies demonstrated that primary BAs exert direct dose-dependent negative myocardial chronotropic effects [61,62]. Secondary BAs activate sphingosine-1-phosphate receptor (S1PR) 2, which promotes apoptosis or survival signaling. In cardiac fibroblasts, S1PR plays a pivotal role in various physiological activities, including proliferation, remodeling, and differentiation. Furthermore, S1PR participates in endothelial cell responses and mediates peripheral vascular tone in both endothelial cells and smooth muscle cells [63]. UDCA, a secondary BA used in the treatment of cholestatic liver disease, has anti-inflammatory and cytoprotective properties and forms mixed micelles around lipopolysaccharide, helping to improve peripheral blood flow in patients with HF [64]. During HF, edema and impaired barrier function of the bowel wall result in translocation of GM components into the host circulation and endotoxemia, which in turn leads to increased systemic inflammation, further aggravating HF [25,29].

The association between the gut-heart axis and HF is therefore attracting increasing attention. Bibliometric analysis is a powerful tool that provides experienced researchers with systematic and visual knowledge structures while also informing novice researchers of the prevailing trends within their field of study [65]. Herein, we present a bibliometric analysis of publications on the gut-heart axis and HF published in the WoSCC database, investigating research dynamics and hotspots in the field.

4.1. General information

A bibliometric analysis using the WoSCC database revealed that 1664 articles related to the gut-heart axis and HF were published from January 1993 to June 2023, involving 9412 authors from 2287 institutions in 86 countries/regions. These articles were published in 761 different journals.

There was a general increasing trend in both the number of publications and citations, indicating the growing interest in this field. This growth aligns with previous studies in the broader field of human GM research [66], as well as the specific subfield focusing on the GM and other CVDs [12,67,68], suggesting that the field of gut-heart axis research will continue to flourish.

Visual analysis revealed that numerous nations and institutions have been actively conducting research on the gut-heart axis and HF, demonstrating the global interest in this field. Notably, the USA has contributed the highest number of publications and is home to several of the most productive institutions, including the Cleveland Clinic, Harvard University, and the University of Pittsburgh. This may in part be attributed to the second phase of the National Institutes of Health-funded Integrated Human Microbiome Program [69]. Chinese institutions have shown increasing participation in this field in recent years.

Professor Tang WHW is a renowned expert in CVD at the Cleveland Clinic, and has the greatest number of publications and citations in the field of the gut-heart axis and HF. Wang Z works alongside Professor Tang WHW and has the fourth highest number of publications and the third highest number of citations. Their team has long been committed to investigating the relationship between the gut-heart axis and CVD. They have examined the impact of the GM on heart health and its correlation with conditions such as HF, and proposed potential treatment strategies [70]. In 2011, they published a groundbreaking article [24] examining the association between the GM, CVDs, and diet. This influential article [24] revealed that three metabolites from dietary phospholipid choline, namely choline, TMAO, and betaine, can be used to predict the risk of CVDs. Further experiments confirmed that these dietary metabolites can promote the development of atherosclerosis, a major cause of CVDs. In atherosclerosis-prone mice, suppression of the intestinal microflora inhibited dietary choline-enhanced atherosclerosis. This study [24] provided new insights into the gut-dependent metabolism of dietary phospholipid choline and its role in the pathogenesis of CVDs. This study also sheds light on how nutrients are metabolized by the GM and their impact on human health, offering potential novel strategies for the prevention and treatment of atherosclerotic CVD. This article [24] is the most cited in the field, demonstrating its importance and influence. Additionally, Tang WHW et al. [27] investigated the relationship between fasting plasma TMAO levels and all-cause mortality in 720 patients with stable HF who were followed up for 5 years. This study [27] revealed that patients with HF and high TMAO levels have a higher long-term mortality risk, independent of traditional risk factors and heart-kidney indices. Notably, this study [27] has the strongest citation burst in this field.

Interestingly, critical care journals, including *Shock*, *Critical Care Medicine*, and *Intensive Care Medicine*, are among the highest publishing journals in the field of the gut-heart axis and HF. Of these, *Shock* has published more articles on the gut-heart axis and HF than any other journal and *Intensive Care Medicin*e had the highest IF (38.9), indicating that critical care medicine may be a current focus of attention for the gut-heart axis and HF and suggesting relatively high-quality literature in this field. Recent evidence has revealed that critically ill patients exhibit altered GM, referred to as pathobiota, which is a prominent contributor to the development of clinical complications. Intestinal overgrowth of pathogenic bacteria, such as *Candida*, *Campylobacter*, *Shigella*, and *Salmonella* was observed in patients with HF and associated with disease severity [29]. In a pilot clinical trial, *Saccharomyces boulardii* supplementation in patients with HF improved the left ventricular fraction and reduced the left atrium diameter [71]. However, the available data remain controversial, potentially due to variations in the levels of dysbiosis observed among the participants included in these studies [71]. Of note, the *Journal of Surgical Research* published the second highest number of articles in the field of the gut-heart axis and HF, revealing that surgical treatment of HF may be one of the current research focuses. Despite significant therapeutic advances, HF remains a progressive disease that, in its advanced stages, is associated with considerable mortality and morbidity. For patients with advanced HF who require cardiac replacement therapy, only two options are available: left ventricular assist device (LVAD) implantation and heart transplantation (HT) [72]. However, a recent study [73] has demonstrated that microbial perturbations persist long-term following LVAD and HT, along with residual inflammation and oxidative stress. Moreover, there is an increasing recognition of the critical role of the microbiome in the metabolism of immunosuppressive drugs after HT.

Circulation, *The New England Journal of Medicine*, *Journal of the American College of Cardiology*, and *Nature* were the most co-cited journals, reminding scholars interested in this topic to pay particular attention to these journals. *Shock*, which has published the highest number of articles, and *Circulation*, which has the highest number of citations, have different emphases. The former primarily covers research related to critical illness, shock, and acute injury, while the latter is one of the top journals in the field of cardiovascular research, emphasizing cardiovascular epidemiology, pathophysiology, and pharmacology. *Circulation*, renowned for its expertise and extensive coverage in cardiology [65], has unsurprisingly received the highest number of citations in the field of the gut-heart axis and HF.

4.2. Hotspots and frontiers

Keyword analysis is a crucial step in exploring research hotspots and predicting future directions [74]. In this study, the keyword analysis identified three keyword clusters, representing three main research directions (Fig. 6A).

One cluster (green cluster) was dominated by “heart failure,” “gut microbiota,” “cardiovascular disease”, “hypertension,” and “obesity,” and mainly focused on the relationship between the GM and various cardiometabolic diseases. In healthy individuals, the GM maintains a relatively stable composition, dominated by a few phyla, including *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Verrucomicrobia*, and *Actinobacteria* [75]. Alterations in the composition of the GM and gut microbial metabolism are linked to the etiology of chronic noncommunicable diseases, including gastrointestinal, cardiovascular, and metabolic illnesses, and cancer [76]. Mounting evidence indicates that the GM plays a significant role in blood pressure regulation and the pathogenesis of arterial hypertension. Clinical studies have demonstrated discernible disparities between individuals classified as prehypertensive or hypertensive and their normotensive counterparts in GM composition, particularly in *Prevotella* and *Klebsiella*, which belong to *Bacteroidetes* and *Proteobacteria*, respectively [77]. Simultaneously, clinical studies have provided evidence for the pivotal role of the GM in fat and sugar metabolism and revealed notable alterations in microbiota composition in individuals with obesity and T2DM [78]. A comparison of fecal bacteria between individuals with chronic HF and healthy individuals demonstrated that the former group exhibited greater colonization of pathogenic bacteria, specifically *Shigella*, *Salmonella*, *Campylobacter*, and *Yersinia enterocolitica,* all of which belong to

Proteobacteria [79], than the latter group.

The second cluster (blue cluster) was dominated by "trimethylamine N-oxide," "metabolism," "risk," "microbiota," "phosphatidylcholine," and "atherosclerosis" and mainly focused on the microbiota and its metabolites. The GM maintains a profound symbiotic relationship with its human host and operates akin to an endocrine organ, generating bioactive metabolites, such as SCFAs, TMA/TMAO, and bile acids. These metabolites contribute to host health through a multitude of pathways [80]. SCFAs, specifically acetate, propionate, butyrate, and malonate, are beneficial GM-derived metabolites produced by the bacterial fermentation of dietary fiber [81] and play a significant role in host immunity and cardiac repair [82]. Acetate [30] regulates hypertension and protects against atherosclerosis. Both propionate [83,84] and butyrate [85,86] have been shown to lower blood pressure, mitigate ischemia/reperfusion injury, and reduce the risk of CVD and atherosclerosis. Although TMAO has long been known, it was not until 2011 that Wang Z et al. suggested that it could be detrimental to human health [24]. Some studies have suggested that TMAO may cause pro-inflammatory responses [87] and apoptosis [88], and disrupt lipid homeostasis [89]. Multiple studies have demonstrated an association between higher plasma TMAO concentrations and an increased risk of atherothrombotic CVD [90,91], HF [41], and adverse outcomes [92].

The third cluster (red cluster) was dominated by "inflammation," "myocardial infarction," "oxidative stress," "mortality," "management," and "gut," and mainly focused on the etiology, pathogenesis, and management of this field. The connection between the gut-heart axis and HF, which represents the interplay between the gut, GM, and HF, refers to cardiac dysfunction resulting in chronic gut hypoperfusion and venous congestion. Subsequently, this leads to reduced nutrient absorption, increased intestinal mucosal permeability, and translocation of microbial products into the systemic circulation, inducing low-level chronic inflammation and dysregulation of the immune system, which further exacerbates HF [9,93]. Furthermore, the GM in patients with chronic HF is characterized by an overall decrease in diversity and anti-inflammatory microbes, particularly those belonging to the *Firmicutes* and *Proteobacteria* phyla [32,94–96]. As the influence of the GM on HF has become better understood, gut microbes and metabolites have become targets for disease prevention and treatment. Strategies include dietary interventions, prebiotic and probiotic therapies, fecal microbiota transplantation (FMT), and antibiotic interventions [41]. For example, a high-fiber diet promotes the growth of acetate-producing microbiota, resulting in reduced blood pressure and attenuated cardiac hypertrophy and fibrosis [30]. Probiotics typically encompass a range of microorganisms including bifidobacteria, yeasts, and lactic acid bacteria. A study in rats demonstrated that the administration of probiotics, specifically *Lactobacillus rhamnosus* GR-1, significantly improved left ventricular hypertrophy and ejection fraction in a model of acute myocardial infarction [97]. FMT is a method of treating intestinal microecological imbalance and restoring normal intestinal function by introducing bacteria or metabolites from the feces of healthy donors into diseased recipients, and is mostly used to treat *Clostridium difficile* infection [41]. While FMT has thus far shown minimal side effects, its effectiveness and safety in treating patients with HF remains uncertain [98]. Additionally, a study in mice showed that injecting antibiotics to eliminate intestinal bacterial translocation alleviated systemic inflammation and myocardial cell damage in a model of myocardial infarction [99].

4.3. Limitations

Our study presents a comprehensive overview of the association between the gut-heart axis and HF. However, it is important to acknowledge the limitations of this study. First, a significant inherent limitation of bibliometric analysis lies in its exclusive emphasis on quantitative metrics, which may not always accurately reflect the genuine impact of certain research work or emerging trends that have not yet garnered a substantial number of citations [55]. Second, we relied solely on the WoSCC database for literature collection, and therefore relevant studies from other databases may have been overlooked. Third, the exclusion of non-English research articles may have introduced source bias. Additionally, owing to the cut-off date of our study, we did not fully evaluate studies published in 2023. Because of the possibility of bias, our findings should be interpreted with some caution.

5. Conclusion

In conclusion, our study revealed that research on the gut-heart axis and HF is increasing steadily. Currently, 86 countries/regions worldwide are involved in this research, led by the USA, China, and Germany. The cooperation between countries/regions and institutions is relatively close. Notably, Professor Tang WHW from the Cleveland Clinic in the United States has made significant contributions to this field, being the most prolific author in terms of publications and citations. Dysbiosis of the GM and metabolic abnormalities are the primary pathways influencing the etiology and pathogenesis of HF. According to the keywords analysis, the mechanism underlying the association between the gut-heart axis and HF remains the focus of research. Moreover, modulation of the GM has the potential to be a significant target for intervention in patients with HF; this may be a promising direction for future research. This study provides researchers with new knowledge and perspectives, which may allow greater clinical application of research findings, expanding the strategies available for disease prevention, diagnosis, and treatment, and maximizing the benefits for patients with HF.

Ethical approval

Because all data used were obtained from the Web of Science database, ethical approval was not required.

Data availability statement

Data included in article/supplementary material/referenced in article. Further data will be made available on request.

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CRediT authorship contribution statement

Jiahui Ouyang: Writing – original draft, Software, Methodology, Formal analysis. **Lingli Zhao:** Writing – original draft, Methodology, Formal analysis. **Yewen Song:** Writing – original draft, Visualization, Methodology, Formal analysis. **Hua Qu:** Writing – review & editing, Methodology, Data curation. **Tianyi Du:** Writing – original draft, Formal analysis, Data curation. **Liu Shi:** Writing – original draft, Software, Formal analysis. **Zhijie Cui:** Writing – original draft, Formal analysis. **Zhonghui Jiang:** Writing – review & editing, Visualization, Software, Methodology, Conceptualization. **Zhuye Gao:** Writing – review & editing, Visualization, Software, Methodology, Data curation.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25995.

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