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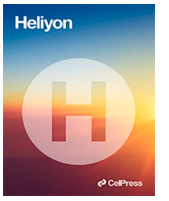

Research article

Evidences and perspectives on the association between gut microbiota and sepsis: A bibliometric analysis from 2003 to 2023

Jiahui Hu [a], Qigu Yao [c], Linjun Zhao [b,*]

[a] Department of Pathology, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou City, 310003, China
[b] Department of Emergency, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, 261 Huansha Rd, Hangzhou City, 310006, China
[c] State Key Laboratory for the Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, National Medical Center for Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Rd., Hangzhou City, 310003, China

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ABSTRACT

Background: In the last two decades, the role of the gut microbiome in the development, maintenance, and outcome of sepsis has received increased attention; however, few descriptive studies exist on its research focus, priorities, and future prospects. This study aimed to identify the current state, evolution, and emerging trends in the field of gut microbiota and sepsis using bibliometric analysis.

Methods: All publications on sepsis and gut microbiota were retrieved from the Web of Science Core Collection and included in this study. VOSviewer, CiteSpace, and the Web of Science online analysis platform were used to visualize trends based on publication country, institution, author, journal, and keywords.

Results: A total of 1,882 articles on sepsis-related gut microbiota were screened, mainly from 95 countries or regions and 2,581 institutions. The United States and China contributed the most to this research field, with 521 (27.683 %) and 376 (19.979 %) articles, respectively. Scientists from the University of California were the most prolific, publishing 63 (3.348 %) articles. Cani PD published papers with the highest H-index, establishing himself as a leader in the field. The most publications were published in the journals "Nutrients" and "PLOS One." The journals with the most co-citations were "PLOS One," "Nature," and "Gut." The most used keywords were prebiotics, gut microbiota, and sepsis. The keyword burst research analysis revealed that research on treatment strategies based on the intestinal microbiota, intestine-liver axis, and regulatory mechanisms of bacterial metabolites are currently hot directions.

Conclusion: This study presents a global overview of the current state and potential trends in the field of sepsis-related gut microbiota. This study identified hot research sub-directions and new trends through comparison and analysis, which will aid in the development of this field.

* Corresponding author.
E-mail address: zlj_0822@126.com (L. Zhao).

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1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis-related mortality is high, with approximately 31.5 million cases reported worldwide annually and in-hospital deaths reaching 30%–50 % [1,2]. Controlling sepsis is challenging owing to its diverse pathogenesis (infection, immunity, tissue damage, and coagulation) [3], the variety of organs involved (the lungs, kidneys, liver, intestines, and nervous system) [4], and the lack of specific treatment methods [5]. Previous studies on sepsis have neglected the crucial role of the gut microbiota in disease progression.

Recently, increasing evidence has revealed that gut microbiome dysbiosis is closely linked to the progression of *Clostridium difficile* infection, necrotizing enteritis, and obesity. Many original research articles have been published, revealing a significant link between the gut microbiota and the occurrence, development, and outcome of sepsis. Disruption of the intestinal microbiome can lead to sepsis progression and severely impact outcomes. For example, two pathogenic exotoxins of *C. difficile,* TcdA and TcdB, damage the human colonic mucosa, causing sepsis and toxic megacolon [6,7]. Necrotizing enterocolitis (NEC) is a devastating disease in preterm infants. Intestinal perforation caused by the disease progression can lead to severe infection and sepsis. Toll-like receptor 4 (TLR4), a bacterial signaling receptor found on intestinal epithelial cells, can influence NEC progression [8]. Obesity is closely associated with metabolic endotoxemia. Ma et al. confirmed that spermidine increased the abundance of short-chain fatty acid (SCFA)-producing bacteria (*Lachnospiraceae* NK4A136 group), significantly enhancing intestinal barrier function and alleviating metabolic endotoxemia [9]. Additionally, gut microbiome-based interventions are increasingly gaining acceptance among patients and healthcare professionals. In a 2017 randomized controlled trial (RCT) to prevent sepsis in rural India, 4,556 newborns who received a synbiotic preparation (*Lactobacillus plantarum* with fructooligosaccharide) exhibited a significantly reduced incidence of sepsis [10]. Furthermore, reports on fecal microbiota transplantation (FMT) in sepsis treatment indicate that FMT transplantation can considerably improve organ function and increase survival rates [11–13].

Gut microbiota research has made significant progress in sepsis susceptibility, gut-organ-related roles, and gut-based microbial therapies [14,15]. Clinical trials, case reports, and basic trials provide ample evidence and commentary [16]. Although many reviews exist on the progress, challenges, and clinical translation of the gut microbiota in sepsis, these reviews often lack objective visual data support and rely heavily on a subjective understanding of the disciplinary framework. Consequently, these reviews exhibit some degree of heterogeneity and subjectivity, limiting our ability to comprehensively understand the current state, priorities, and emerging frontiers in gut microbiota research related to sepsis.

Consequently, bibliometric research and visual analysis were used to summarize the structural characteristics of existing literature in the field, provide the relative contributions of different countries, authors, and journals, and determine the internal correlation between cited and co-cited papers [17,18]. This comprehensive analysis aimed to identify the main research contributions of current studies, investigate emerging sub-directions, assess the current state, and explore the frontiers of the field, thereby establishing a systematic and comprehensive knowledge base.

2. Materials and methods

2.1. Data sources and methods

We searched the Web of Science Core Collection (WoSCC) database for papers on gut microbiota and sepsis. The following were the reasons for including the WoSCC dataset in bibliometrics: First, the WOSCC database currently offers the highest level of evidence and the richest literature, providing a foundation for a large number of high-quality analyses [19,20]. Second, gut microbiota and sepsis are multidisciplinary fields that include microbiology, medicine, pharmacology, and biology. This enables us to have a comprehensive understanding of the association between gut microbiota and sepsis. Third, the WoSCC database offers over 10 types of literature data, including citation reports, which can be directly analyzed using mainstream bibliometric software without the need for format conversion. This reduces the potential impact of data corruption or missing fields. Fourth, the selection of journals in the WoSCC database follows Bradford's and Garfield's laws. The inclusion criteria were as follows: 1) Reviews and original articles; 2) articles written in English; 3) studies providing information on author, title, source, affiliations, year of publication, citations, keywords, research areas, and cited references; 4) studies published between January 1, 2003 and December 31, 2023. The exclusion criteria were as follows: 1) Meeting abstracts, editorial materials, letters, and others; 2) non-English publications. The search formula was: TS = (gut microbe*) OR TS = (gut microflora*) OR TS = (intestinal microflora*) OR TS = (intestinal microorganism*) OR TS = (intestinal microbe*) OR TS = (intestinal microbe*) OR TS = (synbiotics*) OR TS = (prebiotics*) OR TS = (probiotics*) OR TS = (gut metabolites*) OR TS = (fecal bacteria*) OR TS = (gastrointestinal flora*) OR TS = (gastrointestinal flora*) AND TS = (sepsis*) OR TS = (septic shock*) OR TS = (severe sepsis*) OR TS = (SIRS*) OR TS = (systemic inflammatory response syndrome*) OR TS = (endotoxemia*). All searches were completed on the same day to avoid skewing the number of publications caused by database updates.

2.2. Data visual analysis of publications

Microsoft Excel 2019 (Microsoft, Raymond, Washington, US) was used for further processing. Two researchers independently performed data extraction, reference selection, and analysis to ensure the reliability of the results. Subsequently, BioRender (www.biorender.com) was used to create flowcharts, and Microsoft Excel 2019 was used to create statistical tables and trend graphs. H-index, impact factor, and journal classification were collected from the WOSCC database. Bibliometric analysis and visualization of countries, institutions, authors, journals, keywords, and references were conducted using Vosviewer (version 1.6.20) and CiteSpace

(version 6.2. R4) [21,22]. CiteSpace was developed by Professor Chaomei Chen of the School of Computing and Information at Drexel University [23]. It is a mainstream tool for bibliometric research. This study used CiteSpace to analyze parameters, including countries, institutions, keywords, references, and topics, as well as perform cluster visualization and burst detection. VOSviewer was developed by Ike and Waltman of Leiden University. It constructs and visualizes bibliometric networks using the Java framework. This study used VOSviewer to analyze parameters, including countries or regions, institutions, keywords, and references, as well as perform cluster visualization.

Finally, we reviewed all data and tables, revising overlapping items and spelling errors. The focus was on analyzing the impact of co-authorship, co-occurrence, and co-citation in the field.

2.3. Statistical analysis

The data for this study were extracted from the WoSCC database. Descriptive statistics in Microsoft Excel 2019 were used to provide a comprehensive overview of the bibliometric characteristics.

3. Results

3.1. Overview of publication and citation trends

The study included 2,160 articles. Using the aforementioned exclusion criteria, 1,882 papers were selected for bibliometric analysis. The specific flow chart is displayed in Fig. 1.

The number of publications and citations may reflect the progress and direction of research in a field. The overall growth trend in the number of articles published annually in sepsis research related to intestinal microecology is presented in Fig. 2. From 2003, the number of articles published annually increased steadily. The 1,882 publications were cited 57,184 times (55,738 times after removing self-citations), with an H-index of 143. An exponential growth function was used to evaluate the relationship between cumulative publications and year of publication, which matched the trend in cumulative publication numbers ($R^2 = 0.9714$). Notably, the overall number of citations increased rapidly from 2018, indicating that the study of intestinal flora in sepsis research has attracted increasing attention, become a popular research direction, and reached a period of rapid development.

3.2. Top active countries and institutions

To determine which countries have contributed the most to the field of sepsis-related gut microbiota, we conducted a bibliometric analysis of the countries associated with the publications. Table 1 and Fig. 3A indicate the top 10 countries by the total number of publications. The United States leads with 521 publications, followed by China (376), England (114), Australia (107), and Italy (105). The United States had the most citations (32,544), followed by China (12,023) and France (9,330). Although China ranked second in the number of publications, the average number of citations per publication (31.98) was much lower than that of the United States (62.46), England (63.86), and Australia (51.41), indicating that articles by Chinese scholars have low academic impact and that they need to publish higher-quality, innovative academic papers. Although the total number of publications in France was small (64), the average number of citations (145.78) was very high.

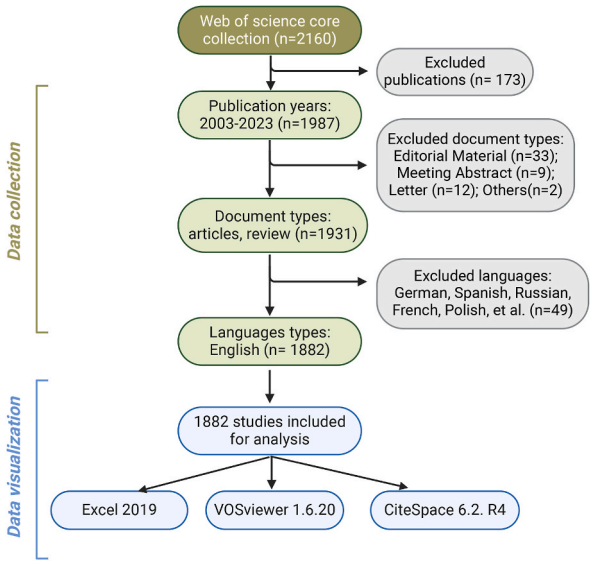

Fig. 1. Flowchart of search and exclusion criteria (created with BioRender.com).

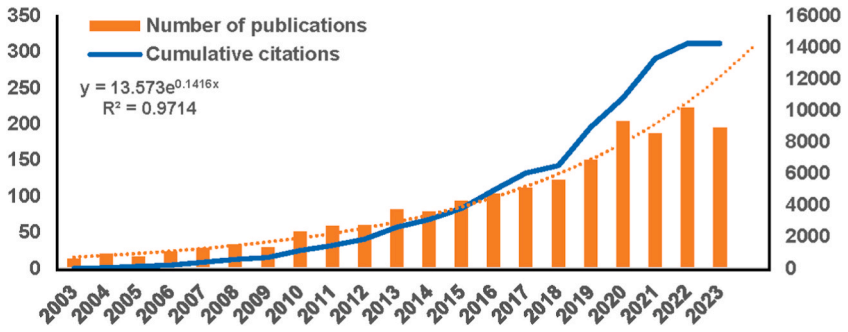

Fig. 2. Trends in the number of publications per year and the cumulative research on sepsis-related gut microbiota.

Table 1
Top 10 countries of publications, H-index, and citations.

Rank	Countries	Publications	Total citations	Average citations	H-index
1	USA (United States)	521 (27.683 %)	32,544	62.46	91
2	Peoples R china	376 (19.979 %)	12,023	31.98	56
3	England	114 (6.057 %)	7,280	63.86	45
4	Australia	107 (5.685 %)	5,501	51.41	39
5	Canada	105 (5.579 %)	4,784	45.56	39
6	Italy	105 (5.579 %)	6,585	62.71	42
7	Germany	92 (4.888 %)	3,682	40.02	37
8	Japan	81 (4.304 %)	3,591	44.33	35
9	India	78 (4.145 %)	1,643	21.06	24
10	France	64 (3.401 %)	9,330	145.78	39

To examine collaborations between countries, we conducted a country analysis of all publications from 95 countries. The node centrality size represents the degree of communication between countries. The United States exhibited a centrality value of 0.27, indicating its pivotal role in paper collaboration and exchange (Fig. 3B). In addition, England (0.18), France (0.14), and the Netherlands (0.13) played significant roles. Fig. S1A demonstrates that the United States and China are central to international collaboration. Germany and France were early pioneers in sepsis-related gut microbiota research; however, researchers in the United States and China have made significant progress in this field in recent years (Fig. S1B).

To assess the 2,581 institutions that have contributed most to the field of sepsis-related gut microbiota, we performed a bibliometric analysis of the institutions in which the papers were published. As depicted in Table 2 and Fig. 3C, the University of California System published the most studies (63), followed by the University of Toronto (35) and the University of London (34). The University of California System and Institut National de la Santé et de la Recherche Médicale demonstrated the most citations, with 5,746 and 3,078, respectively. Fig. 3D depicts that the University of California System, University of London, and Harvard University demonstrated centrality values of 0.09, 0.10, and 0.15, respectively, indicating that they play a bridging role in institutional paper collaboration and exchange. Some institutions in the United States and China emerged from the shadows to play important roles in the field (Fig. S2).

3.3. Top active authors and journals

A total of 10,059 authors participated in sepsis-related gut microbiota studies. Patole S (N = 26), Cani PD (N = 22), and Leelahavanichkul A (N = 20) published the most papers. Cani PD (N = 9,509) and Embleton ND (N = 6,655) were cited much more than other authors, indicating that they are important contributors to this subject (Table 3).

The co-citation analysis of the authors revealed the strength of their associations. Table 4 displays the top 10 co-cited authors. In the visual analysis, VOSviewer grouped co-cited authors with more than 20 citations into five clusters (Fig. 4A). Based on the clustering results, Cani PD, Manzoni P, Bajaj JS, Dickson RP, and Costa RJS are probably the most influential members of their respective international research communities.

Gut microbiota studies of sepsis have been published in 745 journals. Table 5 lists the top 10 journals ranked by publication volume and their recent 2022 Journal Citation Reports (JCR)divisions. Nutrients (N = 60) and PLOS One (N = 40) published the most related content, and the other journals ranked 8–10 published 20–30 articles. These are well-known journals in nutrition, microbiology, gastroenterology and hepatology, and multidisciplinary studies.

The co-citation analysis of journals revealed the strength of their associations. Table 6 presents the top 10 co-cited journals. PLOS One (N = 2,768), Nature (N = 2,663), and Gut (N = 2,016) amassed over 2,000 total citations. Except for the multidisciplinary journal PLOS One, the others are top journals in their specialties. In the visual analysis, VOSviewer grouped co-cited journals with more than 20 citations into five clusters (Fig. 4B). The red cluster, identified as the largest node, comprised Nutrition and Gastroenterology and Hepatology journals, as well as important journals such as Nature, Diabetes, and Gut. The green cluster comprised numerous nodes,

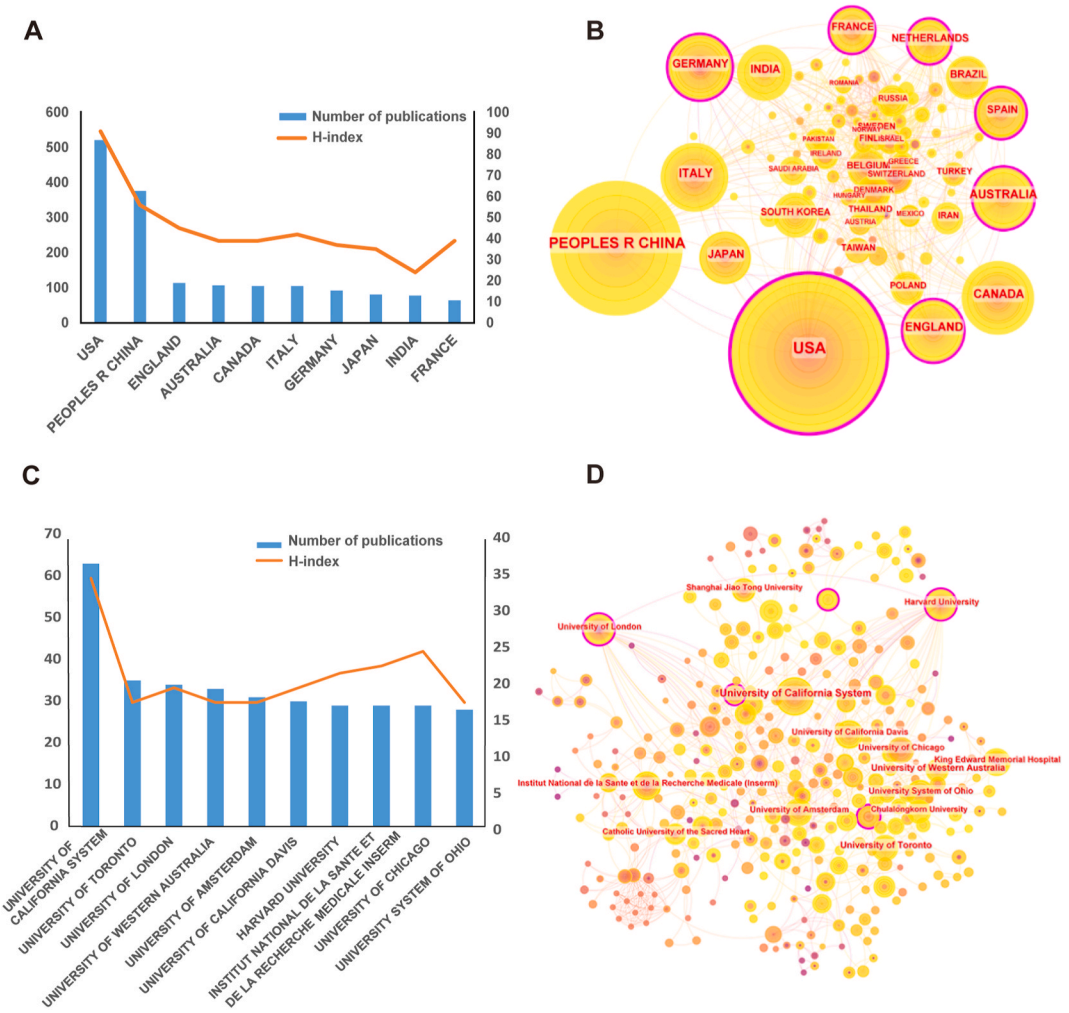

Fig. 3. Distribution of publications and citations by country and institution. (A) Number of citations and H-index rankings for publications from the top 10 countries from 2003 to 2023. (B) Country distribution of publications. Countries with purple rings on the periphery have higher centrality. (C) Number of citations and H-index rankings of publications from the top 10 institutions from 2003 to 2023. (D) Institutional distribution of publications. Countries with purple rings on the periphery have higher centrality.

Table 2
Top 10 institutions of publications, H-index, and citations.

Rank	Countries	Publications	Total citations	Average citations	H-index
1	University of california system	63 (3.348 %)	5,746	91.21	34
2	University of toronto	35 (1.860 %)	994	28.4	17
3	University of london	34 (1.807 %)	1,985	58.38	19
4	University of western australia	33 (1.753 %)	1,477	44.76	17
5	University of amsterdam	31 (1.647 %)	1,573	50.74	17
6	University of california davis	30 (1.594 %)	1,911	63.7	19
7	Harvard university	29 (1.541 %)	1,769	61	21
8	Institut national de la sante et de la recherche medicale inserm	29 (1.541 %)	3,078	106.14	22
9	University of chicago	29 (1.541 %)	2,010	69.31	24
10	University system of ohio	28 (1.488 %)	1,151	41.11	17

including multidisciplinary journals such as PLOS One and Science. The blue cluster focused on general internal medicine, with Critical Care Medicine serving as the representative journal. The yellow cluster focused on clinical and pediatric journals, including Lancet and Pediatrics. The purple cluster focused on microbiology.

Table 3
Top 10 authors of publications, total citations, and H-index.

Rank	Author	Publications	Total citations	H-index
1	Patole S	26 (1.382 %)	1,245	16
2	Cani PD	22 (1.169 %)	9,509	22
3	Leelahavanichkul A	20 (1.063 %)	542	15
4	Alverdy JC	16 (0.850 %)	1,173	16
5	Rao S	15 (0.797 %)	1,184	11
6	Bengmark S	14 (0.744 %)	1,437	13
7	Wang J	14 (0.744 %)	291	6
8	Zhang Y	14 (0.744 %)	289	8
9	Asahara T	13 (0.691 %)	1,046	12
10	Embleton ND	13 (0.691 %)	6,655	12

Table 4
Top 10 co-cited authors of total citations, and H-index.

Rank	Author	Total citations	H-index
1	Cani PD	1,158	22
2	Turnbaugh PJ	446	22
3	Ley RE	345	15
4	Backhed F	330	16
5	Bajaj JS	279	11
6	Manzoni P	267	13
7	Everard A	236	6
8	Lin HC	231	8
9	Alfaleh K	188	12
10	Neu J	181	12

3.4. Keywords: co-occurrence, clusters, and bursts

Keyword analysis revealed hot spots and areas of focus in the research field. The top 20 keywords are presented in Table 7. The three most commonly used keywords were probiotics (542), sepsis (491), and gut microbiota (477). We organized the keywords into three major categories. The first category included synonyms for intestinal microecology; the second category included synonyms for sepsis; and the third category included pathogenic processes and susceptible populations, including infection, inflammation, bacterial translocation, metabolism (obesity and short-chain fatty acids), and NEC and premature infants. This suggests that bacteria, metabolism, and inflammation may be relevant targets for intervention in the intestinal microbiota to treat or prevent sepsis. In particular, a high number of synonyms for prebiotics appeared, implying that prebiotics may be effective in treating or preventing sepsis.

Keyword co-occurrence analysis provided insights into the distribution of topics within the sepsis-related gut microbiota study domain, thereby improving the clarity of specific research content. Fig. 5A depicts a visual representation of the keyword network, revealing the presence of six distinct clusters. The red cluster focuses on the description of the mechanism and clinical manifestations of sepsis, including bacterial translocation, cytokines, and neutrophils; the green cluster focuses on the connection between intestinal flora and metabolism, and the keywords include obesity, metabolic syndrome, and high-fat diet; the dark blue cluster focuses on the preventive effect of prebiotics on disease; the yellow cluster focuses on the characterization of the liver and intestines, as well as the disease process in the liver-intestinal axis; the purple cluster focuses on the intestinal epithelial metabolic process and pro-inflammatory process; the light blue represents the characteristic changes of intestinal bacteria in disease states.

Fig. 5B illustrates how keyword outbreak analysis can provide insights into keyword popularity trends and temporal distribution. The keywords in the early bursts (2003–2008) were focused mostly on the connection between sepsis and bacteria, including bacterial translocation, *Lactobacillus*, and sepsis. In the mid-term period (2008–2014), the keywords were focused mostly on clinical processes and specific populations, including premature infants, critically ill patients, and patients with obesity. From 2014 to 2023, sepsis research on intestinal flora focused on metabolic mechanisms, with short-chain fatty acids, trimethylamine N-oxide, and protein-coupled receptors being prominent research areas.

3.5. Highly cited publications analysis and co-cited publications references clusters, and bursts

The analysis of cited publications helped to understand the development history and identify important publications in this field by VOSviewer. Table 8 presents the 10 most cited publications in this field. The study by Cani et al., titled “Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice,” was cited 3,357 times. Their main findings revealed that intestinal antibiotic treatment caused microbiota changes that reduced metabolic endotoxemia and LPS content in the cecum of high-fat-fed and ob/ob mice. In addition, based on the interconnections of the cited publications, we identified nine large-scale international collaboration clusters (Fig. 6A). The core papers in these clusters included those by Cani in 2018, Miele in 2019, Clarke in 2010, and Vazin in 2013.

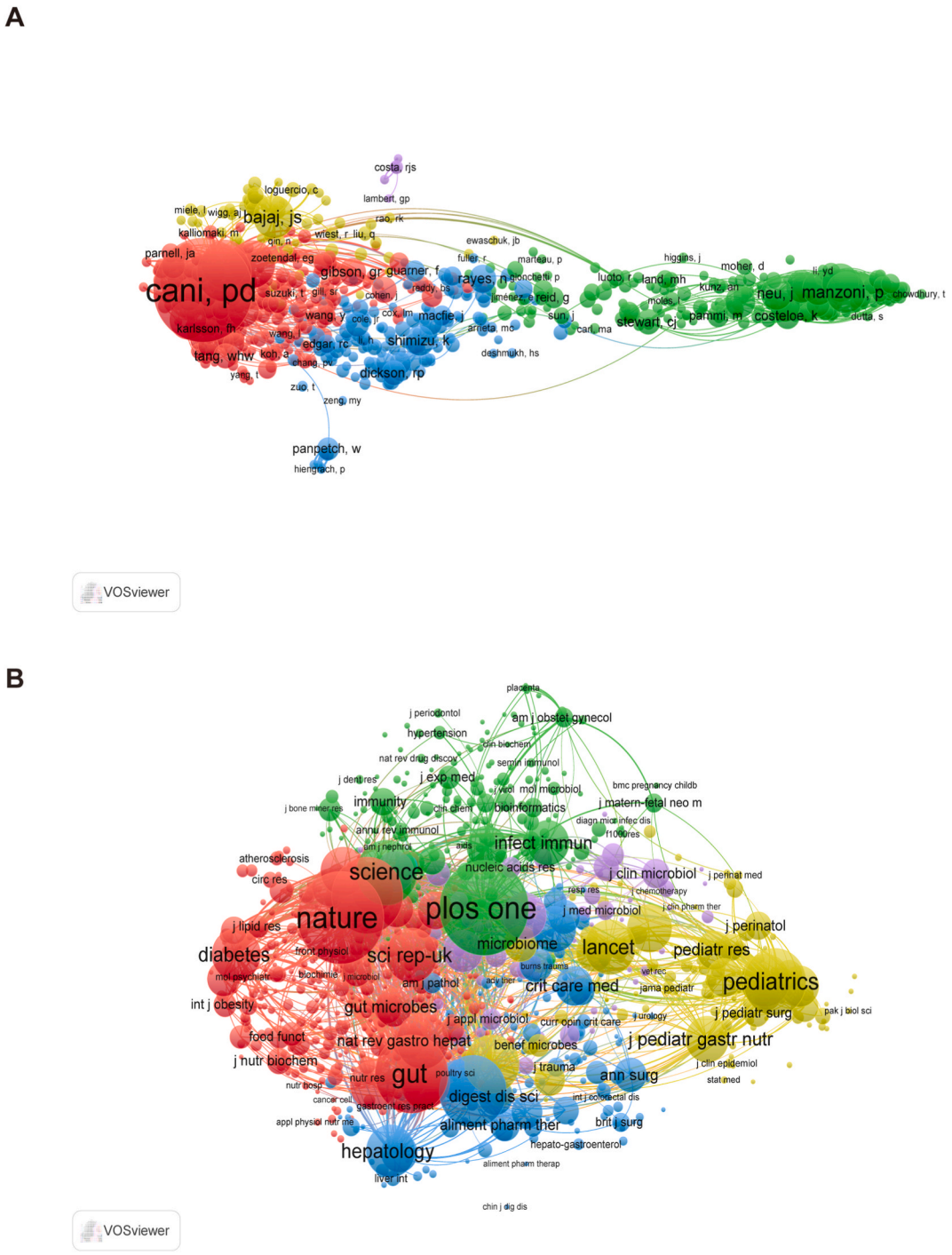

Fig. 4. Visualization maps of co-authors and co-cited journals. (A) Network diagram of author collaborations for sepsis-related gut microbiota research from 2003 to 2023 based on VOSviewer. (B) Network diagram of journals cited for sepsis-related gut microbiota research from 2003 to 2023 based on VOSviewer.

The analysis of co-cited publications helped to identify important publications in this field. The sepsis-related gut microbiota references were categorized into 19 clusters by CiteSpace (Fig. 6B). The top five clusters included cluster #0 necrotizing enterocolitis, cluster #1 preterm infant, cluster #2 insulin resistance, cluster #3 ill patient, cluster #4 preterm neonate. The silhouette suggested that the five clusters were highly credible (S1 = 0.915, S2 = 0.94, S3 = 0.868, S4 = 0.921, and S5 = 0.957). Clusters 0, 2, 7, 8, 10, 11, and 15 are about the common causes of sepsis-related changes in the intestinal microbiota; Clusters 1, 3, and 4 are about susceptible

Table 5
Top 10 journals of publications, JCR.

Rank	Countries	Publications	JCR (2022)
1	Nutrients	60 (3.188 %)	Q1
2	Plos one	40 (2.125 %)	Q2
3	Scientific reports	27 (1.435 %)	Q2
4	International journal of molecular sciences	26 (1.382 %)	Q1
5	Frontiers in microbiology	24 (1.275 %)	Q2
6	Gut microbes	24 (1.275 %)	Q1
7	Frontiers in immunology	22 (1.169 %)	Q1
8	World journal of gastroenterology	22 (1.169 %)	Q2
9	Frontiers in cellular and infection microbiology	21 (1.116 %)	Q1
10	American journal of physiology gastrointestinal and liver physiology	20 (1.063 %)	Q1

Table 6
Top 10 co-cited journal of total citations, JCR.

Rank	Journal	Total citations	JCR (2022)
1	Plos one	2, 768	Q2
2	Nature	2, 663	Q1
3	Gut	2,016	Q1
4	PNSA	1,937	Q1
5	Gastroenterology	1,776	Q1
6	Pediatrics	1,576	Q1
7	Science	1,487	Q1
8	American Journal of Clinical Nutrition	1,275	Q1
9	Nutrients	1,185	Q1
10	Lancet	1,144	Q1

Table 7
Top 20 keywords of publications.

Rank	Keywords	Counts	Rank	Keywords	Counts
1	Probiotics	542	11	Preterm infants	148
2	Sepsis	491	12	Bacterial translocation	139
3	Gut microbiota	477	13	Microbiome	138
4	Inflammation	333	14	Chain fatty-acids	138
5	Endotoxemia	284	15	Infection	138
6	Necrotizing enterocolitis	239	16	Metabolic endotoxemia	135
7	microbiota	227	17	Bacteria	134
8	obesity	223	18	Disease	126
9	Double-blind	211	19	Prebiotics	119
10	Intestinal microbiota	209	20	Late-onset sepsis	118

populations that cause sepsis-related changes in the intestinal microbiota; Clusters 5, 6, 13, 16, and 17 are about the clinical characteristics of diseases that cause sepsis-related changes in the intestinal microbiota; Clusters 9, 12, 14 and 18 are about animal models and research methods that cause sepsis-related changes in the intestinal microbiota.

Subsequently, a clustering timeline map was used to visualize the chronological order of the keywords in the reference titles. As displayed in Fig. 6C, the purple digital label indicates the time when the references appeared. The earlier the circle appeared, the earlier the development of the relevant research subcategory within the cluster. Conversely, the later the circle appeared, the more recent the relevant research subcategory within the cluster was in the research hotspot. This suggests that current gut microbiota studies focus on sepsis caused by NEC and drug-induced liver damage. In addition, cecal ligation has recently become a popular mouse model in sepsis research, where it is used to explore the fundamentals of the condition. As depicted in Fig. 6D, the analysis of reference bursts reveals the trends in sepsis-related gut microbiota research and their duration. The study by Deshpande, G. in 2010, titled "Updated Meta-analysis of Probiotics for Preventing Necrotizing Enterocolitis in Preterm Neonates," demonstrated the highest outbreak intensity score (18.63). The study evaluated the efficacy of probiotics in preventing NEC and sepsis in premature infants. Professor Costeloe, K. published a study titled "*Bifidobacterium breve* BBG-001 in very preterm infants: a randomized controlled phase 3 trial" in *The Lancet*, which became a popular publications between 2016 and 2021. The findings did not support the routine use of *Bifidobacterium breve* BBG-001 in extremely preterm infants to prevent NEC and late-onset sepsis. Rinninella et al., 2019 and Morgan RL et al., 2020 are two recent articles that examined the impact of intestinal flora on septic diseases. Rudd KE et al., 2020 analyzed the global burden of sepsis.

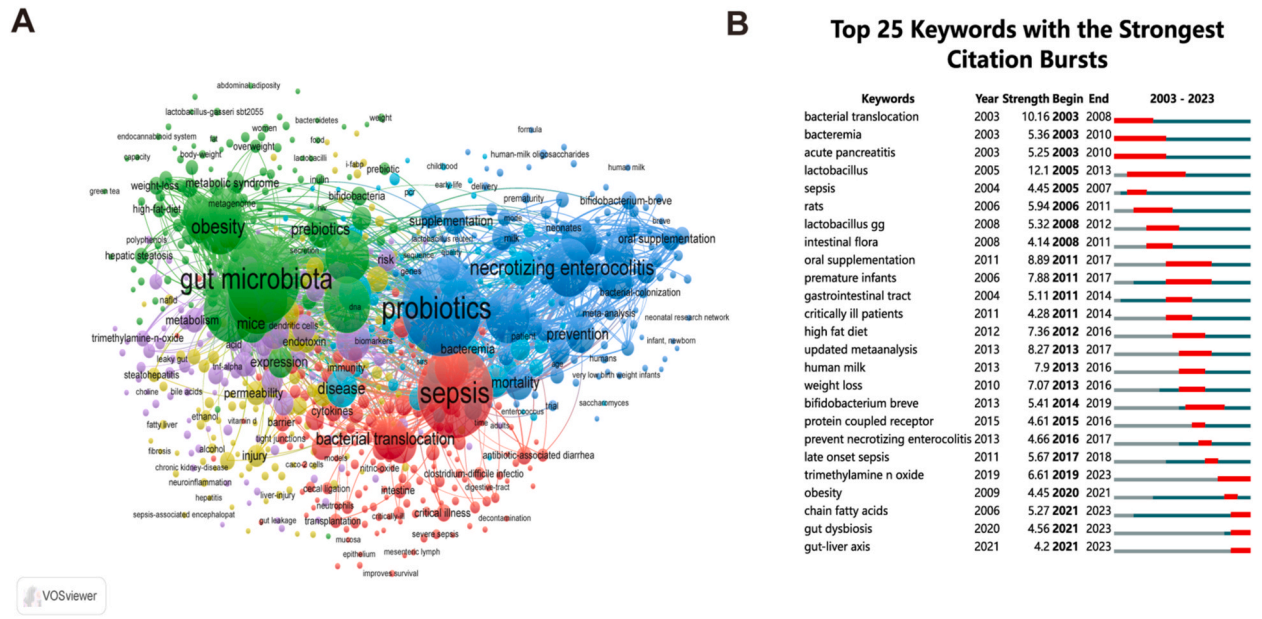

Fig. 5. Research hotspots in sepsis-related gut microbiota from 2003 to 2023. (A) Network map of keywords co-occurrence based on VOSviewer. (B) Top 25 keywords with the strongest citation bursts based on Citespace.

Table 8
Top 10 highly cited publications, JCR, and citations.

Rank	Title	Journal	Authors	JCR (2022)	Citations
1	Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice	Diabetes	Cani, PD	Q1	3,357
2	Increased Intestinal Permeability and Tight Junction Alterations in Nonalcoholic Fatty Liver Disease	Hepatology	Miele, L	Q1	1,001
3	Differential Adaptation of Human Gut Microbiota to Bariatric Surgery-Induced Weight Loss Links With Metabolic and Low-Grade Inflammation Markers	Diabetes	Furet, JP	Q1	886
4	Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity	Nature medicine	Clarke, TB	Q1	838
5	Responses of Gut Microbiota and Glucose and Lipid Metabolism to Prebiotics in Genetic Obese and Diet-Induced Leptin-Resistant Mice	Diabetes	Everard, A	Q1	779
6	Human gut microbiome: hopes, threats and promises	Gut	Cani, PD	Q1	778
7	Ganoderma lucidum reduces obesity in mice by modulating the composition of the gut microbiota	Nature communications	Chang, CJ	Q1	758
8	Chronic kidney disease alters intestinal microbial flora	Kidney international	Vaziri, ND	Q1	743
9	Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models	Gut	Murphy, EF	Q1	673
10	Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation	Am J Physiol-gastr L	de La Serre	Q1	668

Am J Physiol-gastr L: American journal of physiology-gastrointestinal and liver physiology.

4. Discussion

4.1. Research trend of sepsis-related gut microbiota

This study highlights the current state and most popular directions in global sepsis-related gut microbiota research over the last two decades. We analyzed 1,882 documents from the WoSCC database and discovered that the number of publications in this field increased steadily between 2003 and 2009, followed by a rapid increase after 2009. From 2003 to 2013, the total citation count increased gradually, followed by a rapid increase after 2018. The rapid increase in publications and citations demonstrates the continued scholarly interest in this field.

The number of publications serves as the most direct indicator of the expertise of a region or institution in a specific field [24,25]. The majority of the 95 registered countries and 2,581 institutions are located in North America, Asia, and Europe. China and the United States published the most documents, with 376 (19.979 %) and 521 (27.683 %), respectively. However, the United States significantly

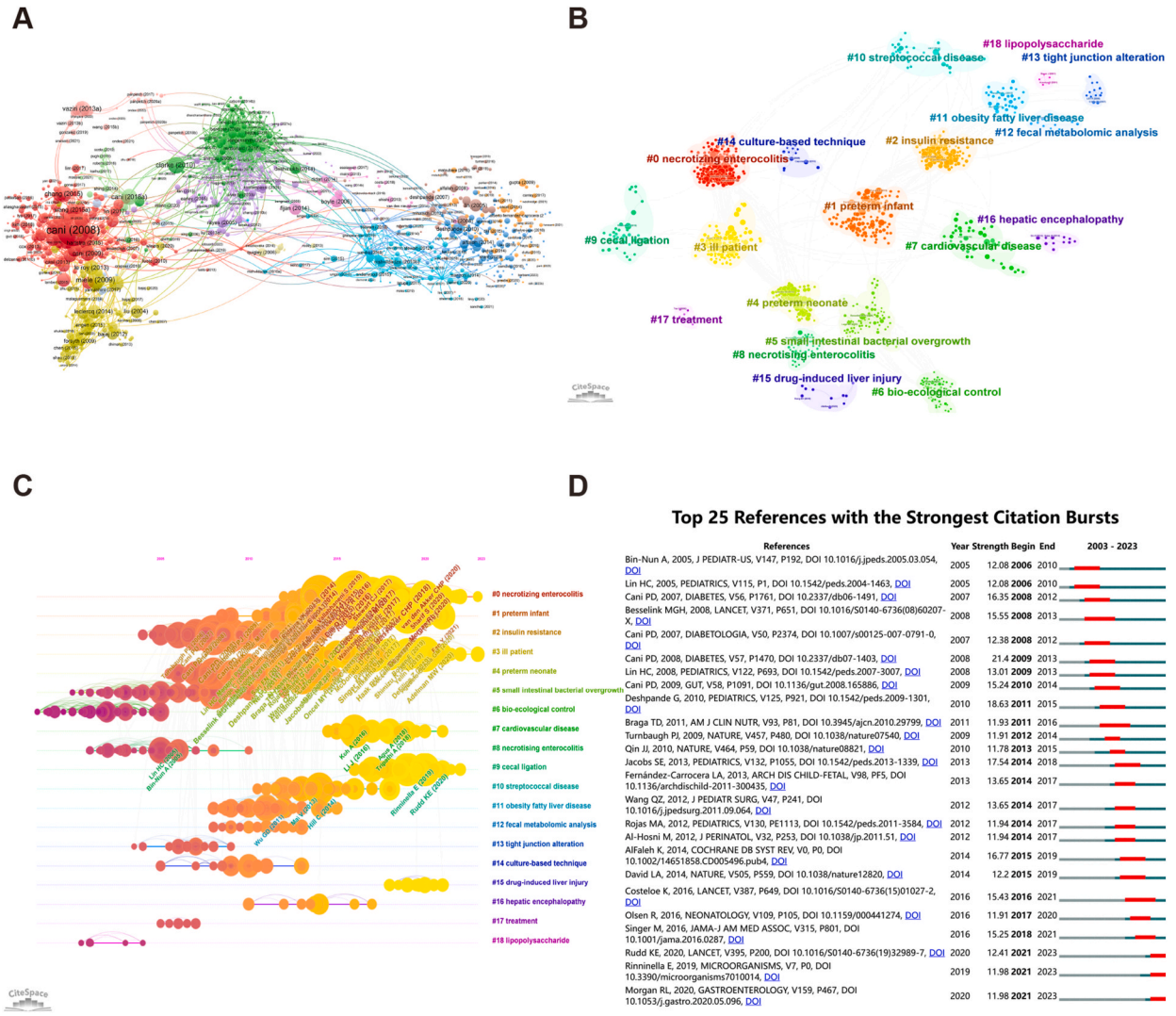

Fig. 6. Research hot publications and references on sepsis-related gut microbiota. (A) Network map of cited publications based on VOSviewer. (B) Cluster network diagram. Based on Citespace, the same color represents belonging to a cluster, and the maximum likelihood ratio method is used to obtain cluster labels based on the words in the title and abstract of the publications under the cluster. (C) Cluster timeline diagram. The later appearance of the circle indicates that the relevant research subcategory of the cluster has remained a research hotspot in recent years. (D) Top 25 references with the strongest citation bursts based on Citespace.

outperformed China in total citations (32,544), average citations (62.46), and H-index (91). Additionally, co-citation analysis revealed that the United States exhibited the highest centrality (0.27), surpassing England (0.18), France (0.14), and the Netherlands (0.13). Prominent American institutions such as the University of California system, the University of California Davis, Harvard University, the University of Chicago, and the University System of Ohio ranked in the top 10 in terms of publications. These results place the United States as the leading research force in this field, likely owing to its stable research foundation and substantial human and financial resources [26]. Furthermore, as an English-speaking country, the United States serves as a central hub for research exchange across Europe and North America, reinforcing its leadership position in the field [27].

The most prominent scholars and their specialized sub-fields can be recognized by examining the number of publications, citation counts, and co-citations [28]. For example, Cani PD, the French author with the highest H-index in this field and affiliated with NeuroMicrobiota, INSERM, studied the relationship between gut microbiota and metabolic endotoxemia in obesity [29–31]. He discovered that low-grade inflammation, which is characteristic of diabetes and obesity, could be mitigated by changes in the gut microbiota caused by antibiotic treatment, thereby reducing metabolic endotoxemia [32]. Further research by Cani PD revealed a connection between the G protein-coupled receptor GPR43 and endotoxemia [33]. Patole S., from the University of Western Australia, conducted numerous meta-analyses on the benefits of using prebiotics in preterm infants [34–37]. In 2007, Patole S discovered that probiotics may reduce the risk of NEC in infants born before 33 weeks of gestation [38]. In 2017, he further demonstrated that probiotics could decrease mortality and morbidity rates among preterm infants in low- and middle-income countries [39].

Leelahavanichkul A. has contributed to understanding the bacterial mechanisms in the gut during sepsis [40–43]. Using iron-overloaded β-thalassemia mice, he demonstrated that gut leakage can exacerbate the severe inflammatory response of macrophages during sepsis [44]. Additionally, *Lactobacillus rhamnosus* L34 reduced FITC-dextran intestinal translocation, serum interleukin-6 (IL-6) levels, and gastrointestinal leakage, ultimately lowering sepsis mortality in cecal ligation and puncture (CLP) mouse model [45]. In summary, these scholars have made significant contributions to the field of sepsis-related gut microbiota and are expected to continue achieving important milestones in this area.

The burst detection feature of CiteSpace identifies hot topics or frequently referenced literature over time [46]. From 2003 to 2013, the keywords "bacterial translocation," "bacteremia," "acute pancreatitis," and *Lactobacillus* were particularly common, indicating that clinical symptoms and bacterial destruction mechanisms in sepsis were key research focuses at the time. For example, Rittirsch and colleagues developed a standardized procedure for inducing sepsis in mice and rats by allowing bacteria to translocate to the blood compartment, triggering a systemic inflammatory response [47]. A 2004 RCT discovered that synbiotics containing *Lactobacillus* La5*, Bifidobacterium* Bb-12*, Streptococci thermophilus, Bulgarian lactobacillus,* and oligofructose improved the upper gastrointestinal microbiota composition in patients with sepsis without affecting intestinal permeability [48]. Recent research on sepsis-related gut microbiota has focused on "chain fatty acids," "gut dysbiosis," and the "gut-liver axis." Lou and colleagues discovered that FMT and SCFAs could modulate the abundance of bacteria such as *Clostridium, Shigella,* and *Lactobacillus* in septic mice, increase colonic Occludin protein expression, downregulate NLRP3 and GSDMD-N protein expressions, and reduce the release of inflammatory factors IL-1β and IL-18 to inhibit pyroptosis, thereby playing a protective role in sepsis [49]. Zhang elucidated the interactive mechanisms and therapeutic potential of the gut-liver axis in sepsis [50]. This demonstrates that over the last five years, gut microbiota research has expanded beyond bacteria to include synergistic mechanisms between the gut and other organs, SCFAs synthesis, and probiotic therapies [51].

4.2. Disrupted gut microbiome predisposes to sepsis

The composition of the gut microbiome is an independent risk factor for sepsis [52,53]. The keyword analysis revealed high-frequency keywords (inflammation and infection), indicating that changes in the composition and quantity of bacterial flora caused by intestinal inflammation can significantly impact the progression of sepsis. Although antibiotics are commonly used to treat sepsis, their usage can disrupt the microbiome, resulting in immune dysregulation and exacerbating the course and outcome of sepsis [54]. A study on the use of broad-spectrum antibiotics in early-onset neonatal sepsis revealed that empirical antibiotics are associated with adverse gut side effects [55]. In neonates, a higher ratio of aerobes to facultative anaerobes can lead to late-onset bloodstream infections [56]. Zhang et al. used mendelian randomization analysis in adults and discovered that the phylum *Lentisphaerae,* class *Lentisphaeria,* and order *Victivallales* were negatively correlated with sepsis, whereas the phylum *Tenericutes* and class *Mollicutes* were positively correlated with the risk of sepsis and death within 28 days. Furthermore, the gut microbiome is critical for survival in sepsis and the host immune response [57]. Lin et al. investigated the relationship between fecal 16S rDNA sequencing and immune indicators in sepsis patients, discovering that *Bacteroides uniformis* was significantly positively correlated with IgM and erythrocyte sedimentation rate, and *Eubacterium eligens* was significantly positively correlated with IL-4 and $CD3^+$ $CD8^+$ T cells [58]. Fay et al. discovered significant differences in immune phenotypes and mortality rates between Jackson and Charles River laboratory mice following CLP, which were attributed to differences in their gut microbiota [59]. Moreover, recolonizing germ-free mice with complex microbiota restored hematopoietic defects and increased resistance to *Listeria monocytogenes* [60]. In keyword analysis, the occurrence of high-frequency keywords (obesity, SCFA, and metabolic endotoxemia) indicates that many different microbial metabolites affect host metabolism, mainly through binding to specific host membranes or nuclear receptors, which has a significant impact on sepsis progression. Additionally, the co-fermentation of indigestible fibers by the commensal gut microbiota, which produces SCFAs, plays a regulatory role. In sepsis, SCFAs can protect intestinal epithelial cells [61], regulate M1/M2 polarization of intestinal macrophages [62], and improve the clearance of pathogenic *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* in the intestinal lumen [63].

4.3. Microbiome-based therapies

Keyword analysis can reveal the hotspots and foci in the research field. Probiotics (N = 542) appeared the most. Over the last three decades, the association between improvements in the gut microbiome of critically ill patients and positive outcomes has become increasingly clear [64–66]. A diversified and balanced intestinal microbiota enhances host immunity against pathogens in the gut and throughout the body [67]. In 2017, an RCT by Panigrahi et al. demonstrated that oral administration of a synthetic probiotic (*Lactobacillus plantarum* plus *fructooligosaccharide*) to 4,556 Indian infants significantly reduced the incidence of sepsis and mortality [10]. Meta-analyses conducted in 2020 and 2023 concluded that probiotics, prebiotics, or their combination could reduce morbidity and mortality in preterm infants, with specific combinations of *Lactobacillus* spp. and *Bifidobacterium* spp. demonstrating moderate to high-quality evidence of reducing all-cause mortality [68,69].

Furthermore, potential microbiome-based therapies were highlighted in the highly high-impact article "Human gut microbiome: hopes, threats, and promises," published by Cani PD. Specific probiotic species, such as *Akkermansia muciniphila*, have been shown to be effective in intervening during the pro-inflammatory phase caused by sepsis. *Akkermansia muciniphila* secretes Arg-Lys-His, which can directly bind to and block TLR4 signal transduction in immune cells [70]. Costeloe et al. reported the effectiveness of *Bifidobacterium breve* BBG-001 in reducing NEC, late-onset sepsis, and mortality in preterm infants [71].

In this field, FMT is not one of the top 20 keywords. FMT involves transferring minimally processed feces from a healthy donor to a

patient with sepsis, which may allow for a more robust restoration of the gut microbiome [72,73]. This can improve sepsis outcomes and reduce late mortality through various mechanisms, including promoting SCFAs, enhancing the intestinal barrier, and modulating the immune system. Studies by Gai et al. and Assimakopoulos et al. revealed that FMT can reduce morbidity and mortality in septic mice by lowering systemic levels of endotoxins, IL-6, and IL-10, as well as restoring microbial abundance and diversity, reducing epithelial cell apoptosis, and improving the mucus layer composition [74,75].

Several case studies have reported on the ability of FMT to restore host immune responses and aid in the recovery of patients with sepsis. For example, a study by Li et al. documented a 44-year-old woman who experienced septic shock following a blood vessel resection surgery. Following FMT treatment, the *Firmicutes* population increased while inflammatory markers decreased [76]. Wei et al. reported on two patients treated with FMT for multiple organ dysfunction syndrome, septic shock, and acute watery diarrhea, highlighting that restoring the gut microbiota barrier could alleviate infection and modulate the immune response [12]. However, advanced research on FMT for sepsis is needed. FMT may increase the risk of pathogen transmission and the incidence of severe adverse effects, as evidenced by two patients in Massachusetts who developed drug-resistant *Escherichia coli* bacteremia following FMT [77].

4.4. Limitations

Bibliometric analysis can be used to track research progress and identify emerging trends in gut microbiota in sepsis. However, this research approach had limitations. 1) To ensure the precision and credibility of literature statistics, we only included articles written in English and documented in the WoSCC database within the last two decades, which slightly affected the overall trend of the results. Additionally, using a single database might have slightly skewed the results. 2) Second, the recently published high-quality studies might not have received the attention they deserved owing to delayed citations. 3) The limitations of the different bibliometric research algorithms, data identification, and version updates could not be ignored. Because this study used manual correction, various software analyses, and other methods to reduce the bias caused by the aforementioned limitations, the overall bias was controlled.

5. Conclusions

This study used bibliometric tools to collect and analyze sepsis-related gut microbiota research over the last two decades. Currently, global scientific output is unevenly distributed, with most developed countries or regions and a few developing countries or regions dominating the field. Our study revealed promising future directions in sepsis research, including the composition of the gut microbiota in patients with sepsis, mechanistic studies of bacterial metabolites, and prebiotic drug development.

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Ethics approval and consent to participate

As this was a bibliometric study, it did not involve the collection of primary data from humans or animals. Ethical approval was not required for this study.

Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Jiahui Hu: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Qigu Yao:** Data curation. **Linjun Zhao:** Writing – review & editing, Funding acquisition.

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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The Figure were created with BioRender.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37921.

List of abbreviations

NEC	Necrotizing enterocolitis
FMT	Fecal microbiota transplantation
IF	Impact factor
WoSCC	Web of Science core Collection database
sEONS	Early-onset neonatal sepsis
CLP	Cecal ligation and puncture
SCFAs	Short-chain fatty acids
RCT	Randomized controlled trial
MR	Mendelian randomization
TLR4	Toll-like receptor 4
MODS	Multiple organ dysfunction syndrome

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