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REVIEW

Global Research Trends in Sepsis-Associated Coagulopathy: A Web of Science-Based Bibliometric Analysis (2000–2024)

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Background: Sepsis-induced coagulopathy (SIC) is a critical determinant of organ dysfunction and mortality in patients with sepsis. While research in this field is rapidly expanding, a comprehensive, quantitative analysis of its knowledge landscape is lacking. This study aims to conduct a bibliometric analysis to delineate the global research status, identify thematic hotspots, and reveal emerging frontiers in the field of SIC from 2000 to 2024.

Methods: We retrieved publications related to SIC from the Web of Science Core Collection (WoSCC), with the final search conducted on May 27, 2025. Only original English-language 'Articles' were included. Bibliometric analysis and knowledge mapping were performed using VOSviewer (v1.6.18) and CiteSpace (v6.2.R6) to analyze countries, authors, journals, co-cited references, and keywords.

Results: A total of 1715 publications were included. The annual publication volume showed an exponential growth trend, particularly after 2020. The United States was the leading country in publication output (471 articles, 27.5%), and Critical Care Medicine was the most productive journal (106 articles). The PROWESS trial published by Bernard GR et al (2001) was the most co-cited foundational document with 4,188 co-citations. Keyword analysis identified four major research clusters: (1) Pathophysiological Mechanisms and Endothelial Injury, (2) Diagnostic Biomarkers and Prognostic Assessment, (3) Anticoagulant Therapy and Clinical Management, and (4) Immunothrombosis and Neutrophil Extracellular Traps (NETs).

Conclusion: Over the past two decades, research on SIC has evolved from exploring fundamental coagulation pathways to investigating the intricate mechanisms of immunothrombosis. Current research hotspots focus on endothelial injury, NETs, and the development of precise diagnostic and therapeutic strategies. This analysis provides a quantitative map of the knowledge structure and emerging trends in the SIC field, offering a valuable reference for future research priorities.

Keywords: sepsis, sepsis-induced coagulopathy, bibliometric analysis, immunothrombosis, neutrophil extracellular traps, NETs, research trends

Introduction

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, remains a paramount global health challenge.[1] Despite decades of medical advancement, it continues to be a leading cause of morbidity, mortality, and healthcare expenditure worldwide, posing a formidable threat to human health.[2–5] The essence of sepsis lies not merely in the infection itself, but in the host's chaotic and self-destructive response. Within this intricate pathophysiological network, coagulopathy emerges not as a late-stage complication, but as a core engine driving the progression towards multiple organ dysfunction syndrome (MODS) and death.[6–8]

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This pathological coagulation activation is now understood as a central component of a deeply intertwined process known as thromboinflammation or immunothrombosis, where the body's inflammatory and coagulation systems engage in a vicious, self-amplifying cycle.[9–11] Triggered by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), an uncontrolled inflammatory cascade—often termed a "cytokine storm"—unleashes profound damage upon the vascular endothelium. This transforms the normally anticoagulant endothelial surface into a highly prothrombotic state. Concurrently, activated immune cells, particularly neutrophils, release neutrophil extracellular traps (NETs), which provide a scaffold for thrombus formation, further fueling this destructive process.[12–14]The clinical consequence is devastating: the formation of microthrombi throughout the microvasculature obstructs blood flow, leading to tissue hypoxia, organ failure, and a significantly increased risk of mortality.[15,16]

Given its profound clinical impact, Sepsis-Induced Coagulopathy (SIC)—a distinct phenotype of this derangement—has become a focal point of intense research. The development of specific diagnostic criteria, such as the ISTH-SIC score, has enabled earlier identification of high-risk patients, yet effective and targeted therapeutic interventions remain elusive.[7,17,18] Over the past two decades, this clinical and scientific urgency has fueled an exponential growth in academic literature. However, this rapid accumulation of knowledge, spanning from molecular biology to critical care medicine, presents a new challenge: the research landscape has become vast, complex, and potentially fragmented. For clinicians and researchers, systematically grasping the core knowledge structure, tracking its evolutionary trajectory, and identifying the most promising frontiers for future investigation is increasingly difficult.

Bibliometrics, a discipline that employs quantitative methods to analyze scientific literature, offers a powerful lens to navigate this complexity.[19–22] By visualizing the intricate networks of authors, institutions, keywords, and citations, it can construct a panoramic map of a research field. Therefore, this study aims to apply bibliometric methods to comprehensively analyze the global research on sepsis and coagulation dysfunction from 2000 to 2024. Through this analysis, we seek to: (1) quantify the growth of publications and identify the leading contributors; (2) map the core research themes and their evolution over time; (3) assess the international collaboration networks; and (4) identify emerging research frontiers, ultimately providing a valuable evidence-based guide for the scientific community to accelerate progress in this critical field.

Material and Methods

This study employed a bibliometric approach, complemented by visualization analysis tools, to systematically evaluate the academic literature in the field of sepsis and coagulation dysfunction over the past two decades.

Data Source and Search Strategy

All literature data for this study were retrieved from the Science Citation Index Expanded (SCIE) database within the Web of Science Core Collection (WoSCC) provided by Clarivate Analytics. The SCIE database was selected as the exclusive data source due to the authoritativeness of its indexed journals, its extensive disciplinary coverage, and the integrity of its citation data, the latter being a prerequisite for conducting co-citation analysis to identify the knowledge base and evolutionary pathways of the field.[22] To ensure data synchronization and reproducibility, all literature searches were completed on a single day, May 27, 2025. The retrieval period was set from January 1, 2000, to December 31, 2024.

To strike a balance between retrieval sensitivity and specificity, this study constructed a Topic Search (TS) strategy designed to comprehensively capture literature directly relevant to "sepsis" and its related concepts, as well as "coagulopathy" and its various terminological representations. The specific search query was as follows:TS= (("sepsis" OR "septicemia" OR "septic shock") AND ("coagulopathy" OR "coagulation disorder" OR "disseminated intravascular coagulation" OR "DIC" OR "hypercoagulable state" OR "thrombo*" OR "thromboembolic disorder" OR "thrombohemorrhagic syndrome")) OR TS= ("Sepsis-Associated Coagulopathy" OR "Sepsis-Induced Thrombosis" OR "Sepsis-Related Coagulopathy" OR "Sepsis-Triggered Coagulopathy" OR "Sepsis-Induced Hemostatic Dysfunction").

Literature Screening and Data Collection

To ensure the quality and consistency of the literature included for analysis, stringent inclusion and exclusion criteria were established. The inclusion criteria were: (1) document type classified as "Article", as these represent the forefront of knowledge innovation in the field; and (2) language specified as "English", to ensure international comparability. The exclusion criteria

encompassed conference abstracts, editorials, news items, book reviews, reviews, corrections, retractions, and other non-original research document types.

The literature screening process strictly adhered to the recommended steps of the PRISMA statement (Figure 1). An initial search yielded 2,838 publications. After applying the aforementioned criteria, 1718 documents were retained. Subsequently, three duplicate records were removed using software, resulting in a final dataset of 1715 publications for subsequent analysis. To ensure the objectivity and accuracy of the screening process, the entire procedure was conducted independently by two researchers (Xiaolin Wang and Zhiming Liu). Any discrepancies were resolved through discussion or consultation with a third party (Corresponding Author's Initials). For each publication ultimately included, the "Full Record and Cited References" containing all data fields was exported from the WoSCC database and saved in plain text format for further analysis.

Bibliometric Analysis and Visualization

This study utilized a suite of bibliometric analysis software to achieve multi-dimensional data parsing and visualization. To ensure transparency and reproducibility, the key parameters were standardized.

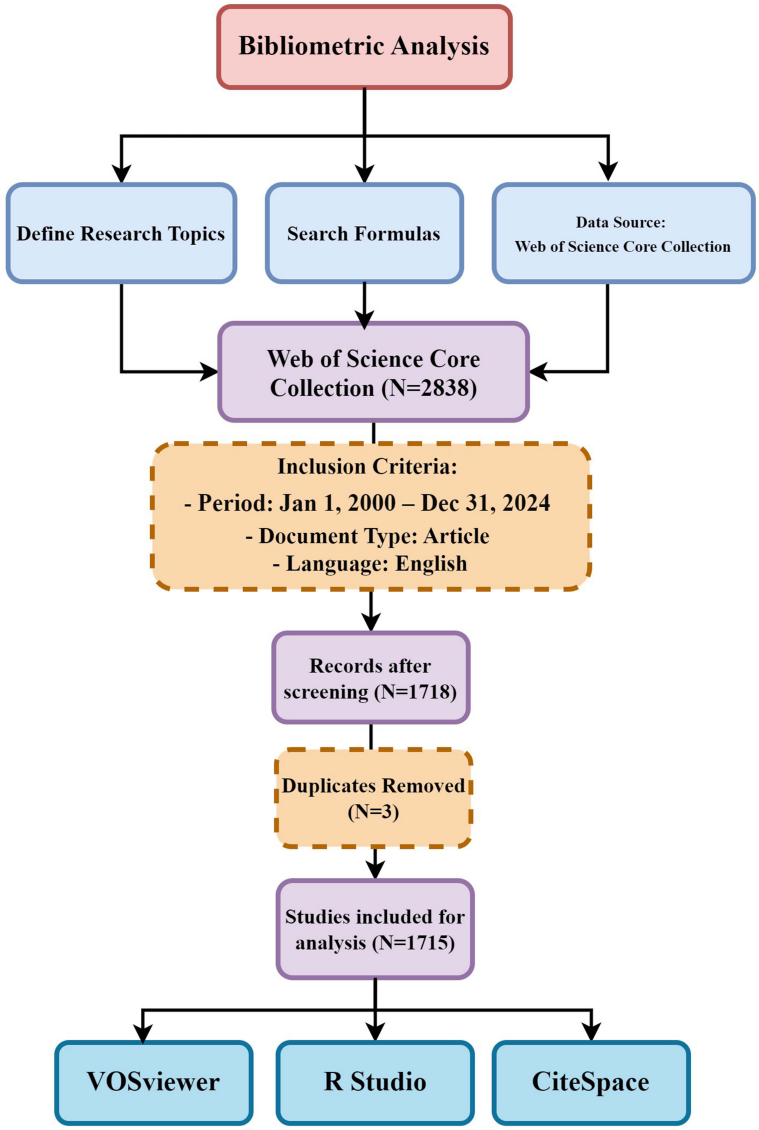

Figure 1 PRISMA Flow Diagram for Literature Screening. The diagram illustrates the step-by-step process of identifying, screening, and selecting the final set of 1,715 publications included in the bibliometric analysis.

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VOSviewer (v1.6.18) was primarily used for constructing and visualizing scientific knowledge networks. For co-authorship and co-occurrence analyses, a minimum threshold was set (eg, a minimum of 5 documents for a country; a minimum of 20 occurrences for a keyword) to ensure the clarity of the maps. The association strength method was used for normalization, and network nodes were clustered using VOSviewer's smart local moving algorithm.

CiteSpace (v6.2.R6) was focused on identifying the knowledge structure and evolutionary dynamics of the field. The time slicing was set from 2000 to 2024 with 1-year slices, and the top N=50 most cited items from each slice were selected. The Pathfinder algorithm was used for network pruning. Keyword clustering was performed using the Log-Likelihood Ratio (LLR) algorithm. For burst detection, a minimum duration of 2 years was set. For the co-cited author analysis, a minimum of 100 citations per author was required, and name variants were disambiguated.

Furthermore, the "bibliometrix" package in RStudio (v4.5.0) was employed for creating the geographical distribution map, and Microsoft Excel 2019 was used for producing the annual publication trend chart.

Results

Analysis of Annual Publication Trends

A total of 1,715 original English-language articles were included in the analysis. The annual publication output, as depicted in Figure 2, demonstrates a clear and sustained upward trend over the past two decades. This growth trajectory

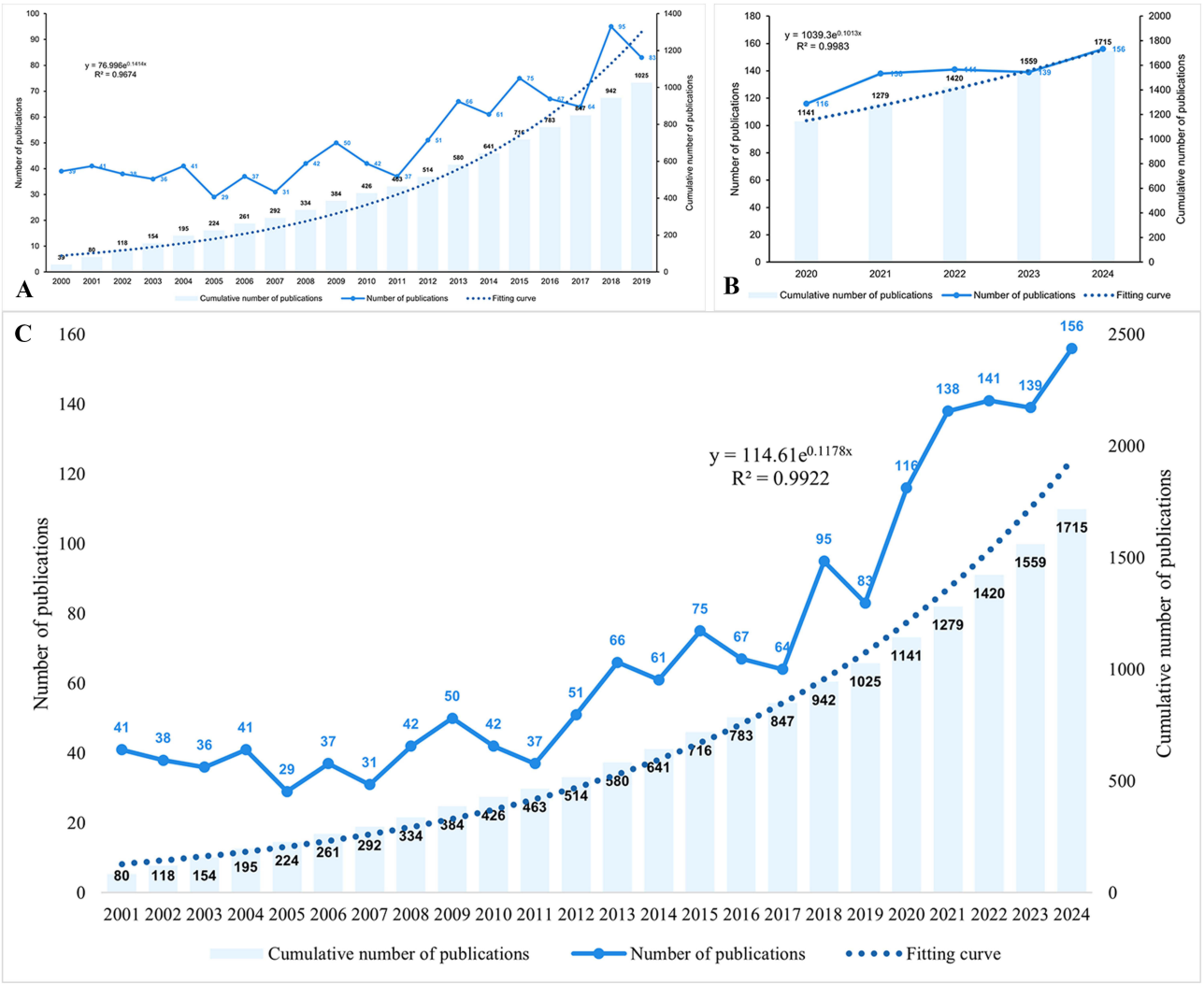

Figure 2 Annual publication trends in the field of sepsis-associated coagulopathy (2000–2024). The dotted line represents the overall exponential fitting curve for the entire period. Sub-charts (**A**) and (**B**) provide a closer look at the publication trends for the periods 2000–2019 and 2020–2024, respectively, highlighting the distinct two-phase growth pattern. The main chart (**C**) displays the annual number of publications (blue line) and the cumulative number of publications (light blue bars).

Table 1 Top 10 Countries/Regions by Publication Volume in Sepsis and Coagulation Dysfunction Research (2000–2024)

Rank	Country	Counts	Percentage	Total Cites	Average Cites	Total Link Strength (VOSviewer)
1	USA	471	27.46%	31,894	67.72	345
2	CHINA	292	17.03%	3983	13.64	72
3	JAPAN	230	13.41%	8108	35.25	88
4	GERMANY	119	6.94%	8531	71.69	130
5	NETHERLANDS	103	6.01%	7221	70.11	137
6	ENGLAND	89	5.19%	6373	71.61	166
7	FRANCE	88	5.13%	11,842	134.57	111
8	ITALY	77	4.49%	3032	39.38	90
9	CANADA	56	3.27%	10,402	185.75	128
10	INDIA	54	3.15%	2011	37.24	53

can be characterized by two distinct phases: a period of steady, fluctuating growth from 2000 to 2019, followed by a marked and steep acceleration in publication velocity from 2020 onwards. This distinct inflection point strongly suggests that a significant catalytic event occurred around 2020, which dramatically intensified research activity in the field. The overall exponential fitting curve ($y = 114.61e^{0.1178x}$, $R^2 = 0.9922$) accurately models the entire period but is heavily influenced by this recent surge, underscoring its profound impact.

Country/Region Level Analysis: Global Research Landscape and Collaboration Networks

Global Publication Distribution and Academic Influence

A total of 47 countries or regions have contributed to research in this field. Among them, the United States leads in both publication volume (471 articles, 27.46% of the total) and total citation frequency (31,894 citations), demonstrating its definitive leadership and formidable academic influence in the domain (Table 1). This global output pattern is visually represented in the geographical distribution map (Figure 3), where the color intensity clearly indicates that North America, East Asia, and Western

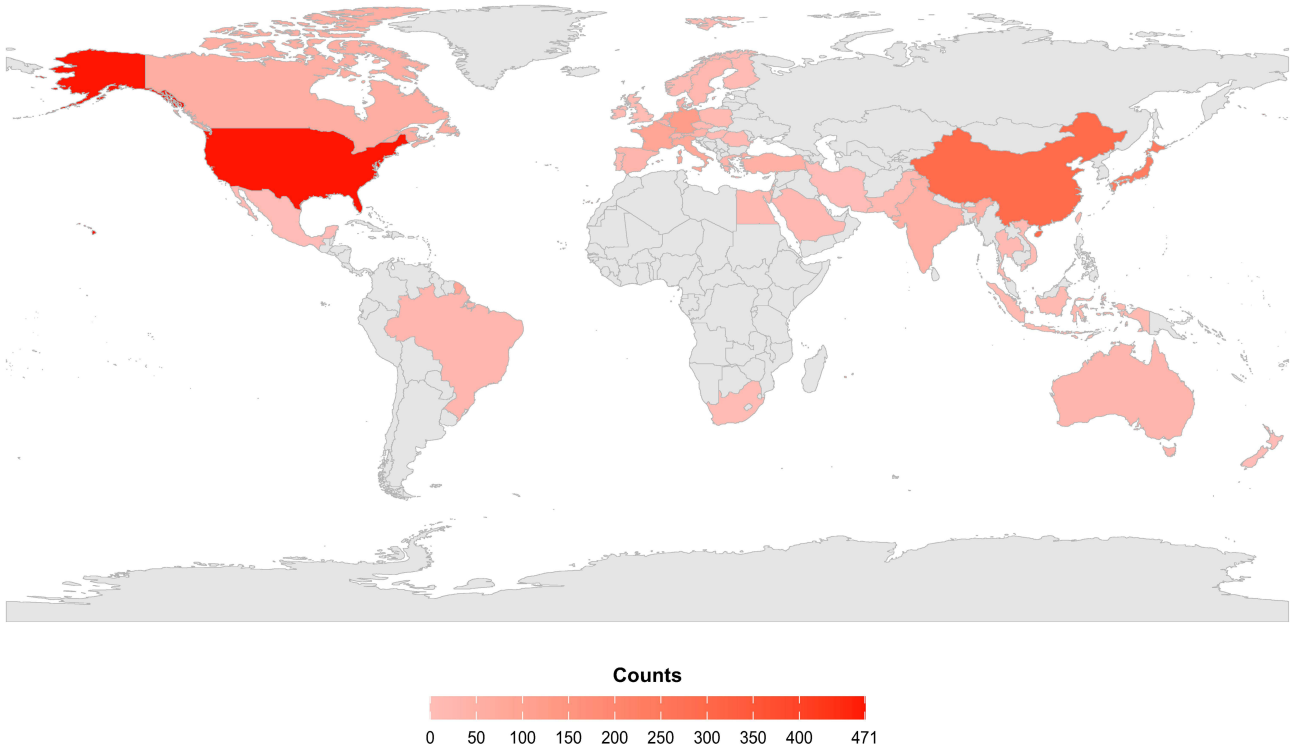

Figure 3 Global geographical distribution map of publication output in sepsis and coagulation dysfunction research. The color intensity of each country/region is proportional to its total number of publications, with darker red indicating higher output.

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Europe are the three core regions with the highest concentration of research activity in this field. This landscape suggests that the United States is not only the primary engine of knowledge production in this field but also likely plays a pivotal role in shaping international guidelines and leading foundational research directions. China (292 articles) and Japan (230 articles) follow, forming the core of Asia's research output. However, China's average citations per publication (13.64) is relatively low among the top 10 countries, indicating that the international impact of its academic output has room for improvement relative to its publication quantity.

In terms of average citations per publication—a metric reflecting research quality and influence—Canada (185.75), France (134.57), and Germany (71.69) exhibit particularly outstanding performance, suggesting that the literature published by these nations possesses a higher average academic quality. The VOSviewer overlay map (Figure 4 reveals that the United States and several European countries initiated research in this field earlier, accumulating a substantial body of work (indicated by nodes in blue and purple hues). In contrast, countries like China and India are emerging scientific powerhouses that have risen rapidly in recent years, with their research activities appearing in more recent colors (yellow) on the map.

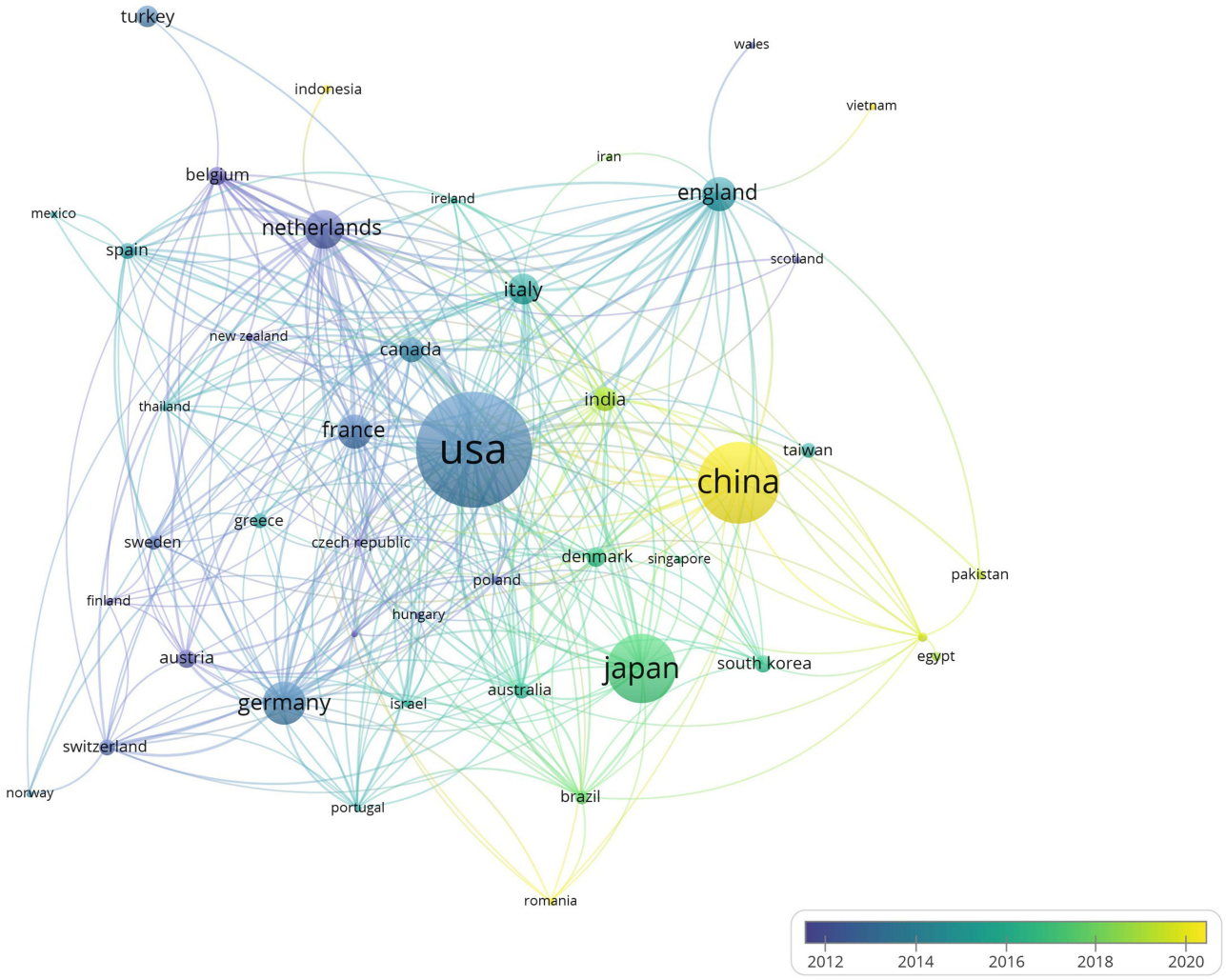

Figure 4 International collaboration network in the field of sepsis and coagulation dysfunction research. The overlay map visualizes the collaboration relationships between countries. Each node represents a country, with the node size proportional to its publication count. The links (edges) between nodes indicate collaboration, and the node color represents the average publication year of that country's output, with colors shifting from blue (earlier) to yellow (more recent).

International Collaboration Network

The international collaboration landscape, visualized in the overlay map (Figure 4), reveals a network centered around the United States, which has the highest total link strength (345) as shown in Table 1. The node colors, representing the average publication year, provide a temporal dimension to this network. Early and foundational research (indicated by purple and blue nodes) originated predominantly from the United States and several Western European countries like Germany and France. These nations not only lead in research output but also act as central hubs connecting global knowledge exchange. In contrast, emerging scientific powerhouses, particularly China (indicated by a prominent yellow node), have significantly increased their contributions in more recent years. The primary channels of collaboration exist between the United States and partners in Europe (United Kingdom, Germany) and Asia (China, Japan), forming a global research consortium that collectively drives the field's advancement.

Co-Cited Author Analysis: Identifying Foundational Scholars and Core Communities

Co-citation analysis identifies authors whose works are frequently cited together by subsequent scholars, often highlighting the field's foundational figures and core authorities. As shown in Table 2, Dhainaut, J.F. ranks first with an impressive 6,040 citations, followed by Bernard, G.R. (5,156 citations) and Vincent, J.L. (4,941 citations). These individuals are internationally recognized as pioneering scholars who have had a profound impact on the field.

To further unveil the academic connections and schools of thought among scholars, we constructed a co-cited author network map (Figure 5). The map reveals four major author clusters, each clearly representing distinct academic communities and research directions:

i. **Red Cluster (Cluster 1)**: Centered around internationally renowned experts in critical care and thrombosis/hemostasis, such as Bernard, G.R., Dhainaut, J.F., and Levi, Marcel. This cluster represents the cornerstone of the field's foundational theories and clinical practices. Their research laid the groundwork for understanding the pathophysiology, diagnostic criteria, and early therapeutic explorations of sepsis-induced coagulopathy.
ii. **Green Cluster (Cluster 2)**: Primarily composed of Japanese scholars, including Gando, Satoshi, and Iba, Toshiaki. This indicates that Japan has established a distinctive and internationally influential research contingent in this field, with prominent contributions in the diagnosis and treatment of DIC and studies based on local clinical data.
iii. **Blue and Yellow Clusters (Cluster 3 & 4)**: Represented by scholars like Opal, S.M., and Fareed, Jawed, respectively. These clusters reflect in-depth explorations of specific mechanisms, such as immunology and inflammation (Opal) and the pharmacology of anticoagulant drugs (Fareed).

These interconnected yet distinct academic communities collectively form the intellectual backbone and developmental trajectory of the research field of sepsis and coagulation dysfunction.

Table 2 Top 10 Co-Cited Authors in the Field of Sepsis and Coagulation Dysfunction Research

Rank	Name	Citations	Total Link Strength	Documents	Avg. Pub. Year
1	Dhainaut, JF	6040	527	13	2002.77
2	Bernard, GR	5156	275	8	2002.38
3	Vincent, JL	4941	245	9	2002.11
4	Opal, Steven M.	2816	119	7	2010.71
5	Vincent, Jean-Louis	2778	181	9	2013.00
6	Van Der Poll, Tom	2111	383	22	2014.95
7	Lupu, Florea	1755	66	9	2013.89
8	Yan, SB	1683	310	11	2002.36
9	Opal, SM	1673	396	7	2003.71
10	Levi, Marcel	1529	455	17	2012.71

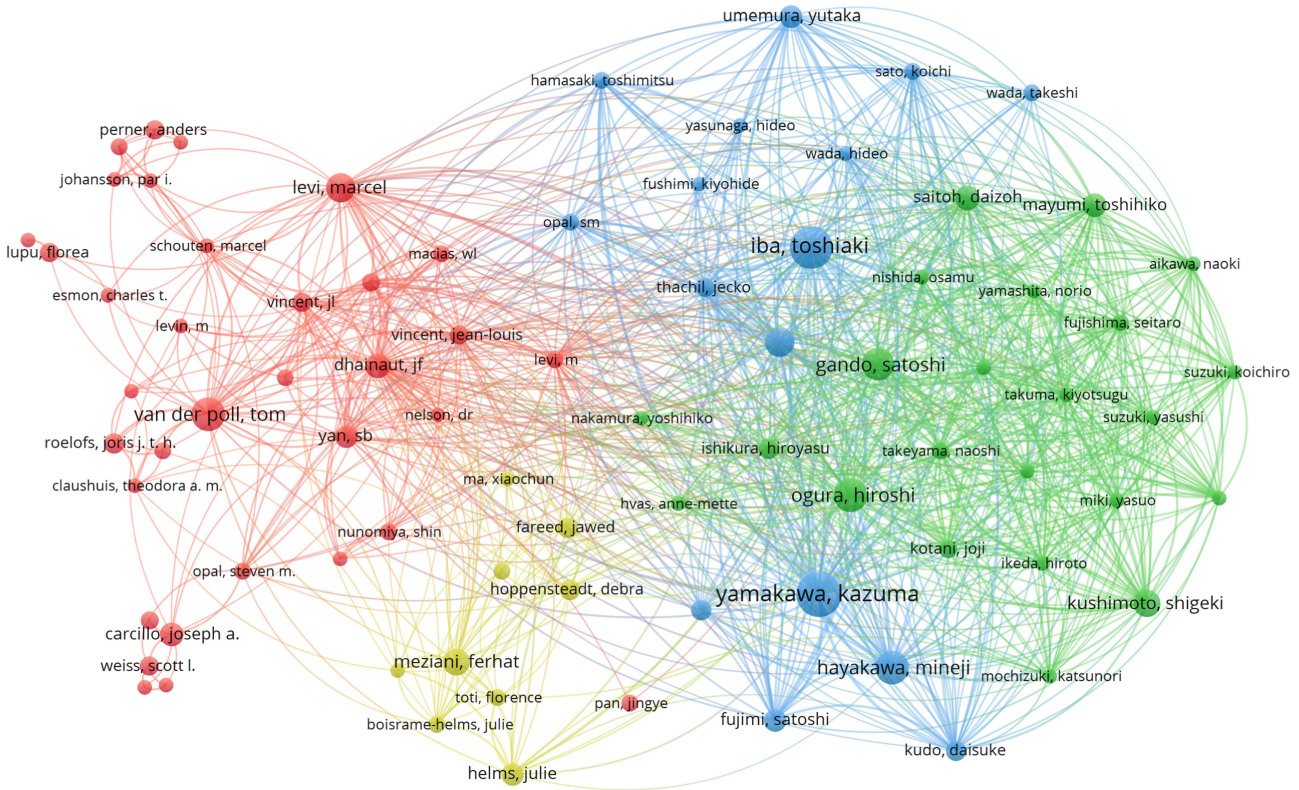

Figure 5 Network map of the main co-cited authors in the field of sepsis and coagulation dysfunction research. Each node represents an author, with the node size proportional to their total co-citation frequency. The links between nodes indicate that the two authors have been frequently cited together. Different colors represent distinct academic communities or schools of thought identified by the clustering algorithm.

Journal Analysis: Identifying Core Academic Platforms and Knowledge Flow

Major Publishing Journals and Academic Influence

The 1,715 articles included in this study were distributed across 607 different academic journals. As shown in Table 3, *Critical Care Medicine* published the highest number of studies in this field (106 articles) and garnered an exceptionally high number of citations, highlighting its definitive leadership position. The journal co-occurrence network map (Figure 6) further reveals the core journal communities in this area. This clustering phenomenon clearly indicates that research output is primarily concentrated on two major knowledge platforms: one is the critical care medicine journal group, represented by *Critical Care Medicine* and *Intensive Care Medicine*, which focuses on clinical practice and

Table 3 Top 10 Journals by Publication Volume in the Field of Sepsis and Coagulation Dysfunction Research

Rank	Journal Name	Documents	Citations in Dataset	IF	JCR
1	*Critical Care Medicine*	106	9684	7.7	Q1
2	*Critical Care*	61	4281	8.8	Q1
3	*Shock*	55	1314	2.7	Q1
4	*Clinical And Applied Thrombosis-Hemostasis*	46	598	2.3	Q2
5	*Thrombosis Research*	42	1099	3.7	Q1
6	*Journal Of Thrombosis And Haemostasis*	40	2378	5.5	Q1
7	*PLOS One*	33	1369	2.9	Q1
8	*Intensive Care Medicine*	31	3401	27.1	Q1
9	*Journal Of Critical Care*	28	735	3.2	Q2
10	*Thrombosis And Haemostasis*	28	1247	5.0	Q1

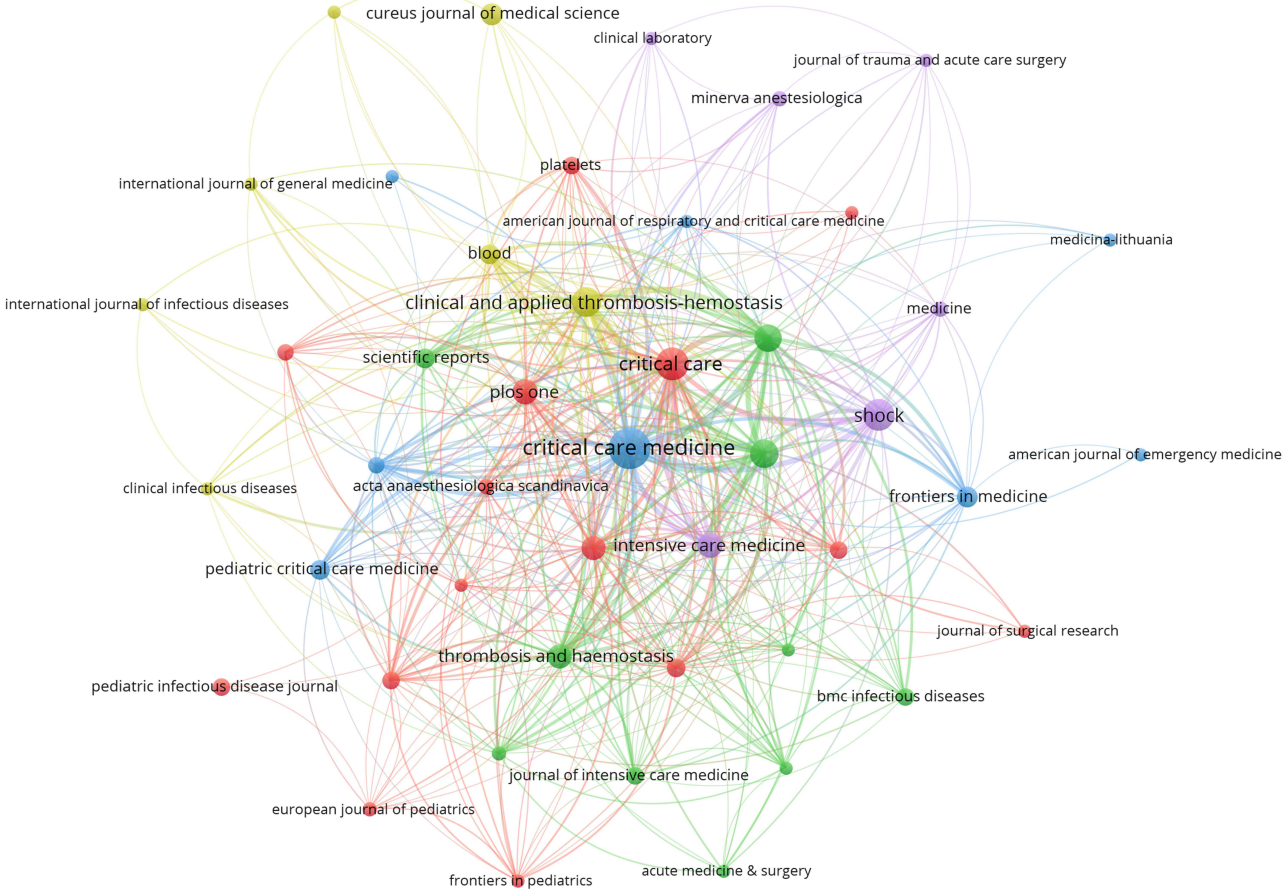

Figure 6 Journal co-citation network map in the field of sepsis and coagulation dysfunction research. Each node represents an academic journal, with its size corresponding to its co-citation frequency. The links between journals indicate their intellectual proximity, established by being frequently cited together in the reference lists of the source articles.

management; the other is the thrombosis and hemostasis specialty journal group, represented by the *Journal of Thrombosis and Haemostasis* and *Thrombosis Research*, which concentrates on pathophysiological mechanisms and therapeutic target exploration. The strong connections between these two platforms reflect the close interaction between clinical problems and basic research.

Journal Citation Relationships: Visualizing the Translational Medicine Pathway

To investigate the flow of knowledge across disciplines, we generated a dual-map overlay of journal citation relationships (Figure 7). This map provides compelling visual evidence of the field's core identity as a quintessential translational medicine domain. The citation pathways, flowing predominantly from left to right, clearly illustrate that research published in basic science journals (labeled under "MOLECULAR, BIOLOGY, IMMUNOLOGY") is extensively cited by journals in the clinical domain (labeled "MEDICINE, MEDICAL, CLINICAL"). This strong directional flow is not merely a collection of citations; it represents a robust knowledge translation chain from "bench to bedside", where fundamental discoveries in immunology and molecular biology directly inform and underpin the clinical research and practice in sepsis-associated coagulopathy.

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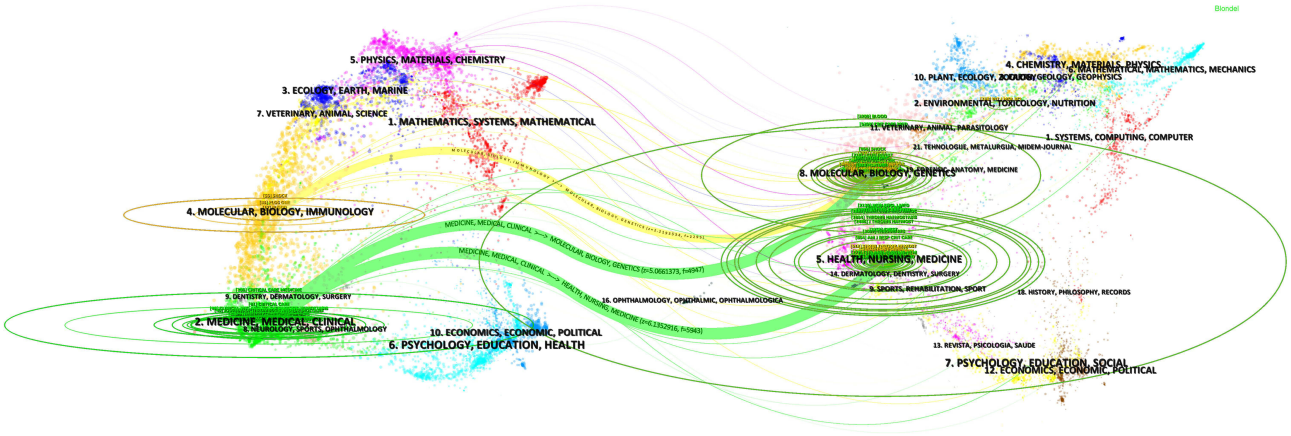

Figure 7 Dual-map overlay of journal citation relationships in the field of sepsis and coagulation dysfunction research. The ovals on the left represent the disciplinary clusters of citing journals, while the ovals on the right represent the clusters of cited journals. The connecting curves (citation links) visualize the flow of knowledge, primarily from basic science disciplines (eg, MOLECULAR, BIOLOGY, IMMUNOLOGY) to clinical disciplines (eg, MEDICINE, MEDICAL, CLINICAL).

Document Co-Citation and Citation Burst: Tracking the Intellectual Cornerstones and Paradigm Shifts

Identification of the Knowledge Base

Document co-citation analysis (Figure 8 and Table 4) identifies the "intellectual cornerstones" of the field. The PROWESS trial on recombinant human activated protein C, published by Bernard GR et al in 2001, stands as the most highly cited foundational literature with 4,188 co-citations, defining an era of therapeutic exploration in the early 21st century. Concurrently, the "Surviving Sepsis Campaign" guidelines, published by Dellinger RP et al, constitute the knowledge core for clinical practice.

Evolution of Research Paradigms

Citation burst analysis (Figure 9) serves as a historical chronicle, clearly delineating the "paradigm shifts" in the field's research focus:[1,8,23–45]

i. **The Era of Early Therapeutic Target Exploration (ca. 2001–2006)**: Represented by the PROWESS trial (Bernard GR, 2001),[43] its remarkable burst strength of 43.0 demonstrates the academic community's immense enthusiasm for and exploration of single, revolutionary anticoagulant targets like activated protein C.

ii. **The Era Driven by Clinical Guidelines and Standardized Definitions (ca. 2014–2021)**: The successive emergence of the Sepsis-3 definition by Singer M (2016)[32] (burst strength 81.9) and the Surviving Sepsis Campaign (SSC) guidelines by Dellinger RP (2013)[35] (burst strength 33.21) marked a paradigm shift from searching for a "magic bullet" to focusing on precise disease definition and standardized clinical management. This profoundly influenced the design of subsequent studies and patient enrollment criteria.

iii. **The Current Era of Macro-Level Evidence and Prognostic Focus (2022–Present)**: Recently bursting literature, such as Rudd KE's (2020)[1] study on the global burden of sepsis and the latest SSC guidelines by Evans L (2021),[24] indicates that the current research focus has shifted to global epidemiological evidence, the integration of the latest clinical practices, and a heightened concern for patients' long-term outcomes.

Keyword Analysis: Decoding Core Themes

To reveal the internal structure of research themes, we conducted a keyword cluster analysis. After manually reviewing the constituent keywords within each major cluster, we assigned meaningful academic labels. The resulting keyword clustering map (Figure 10) identifies eleven principal research clusters that delineate the field's core intellectual landscape.

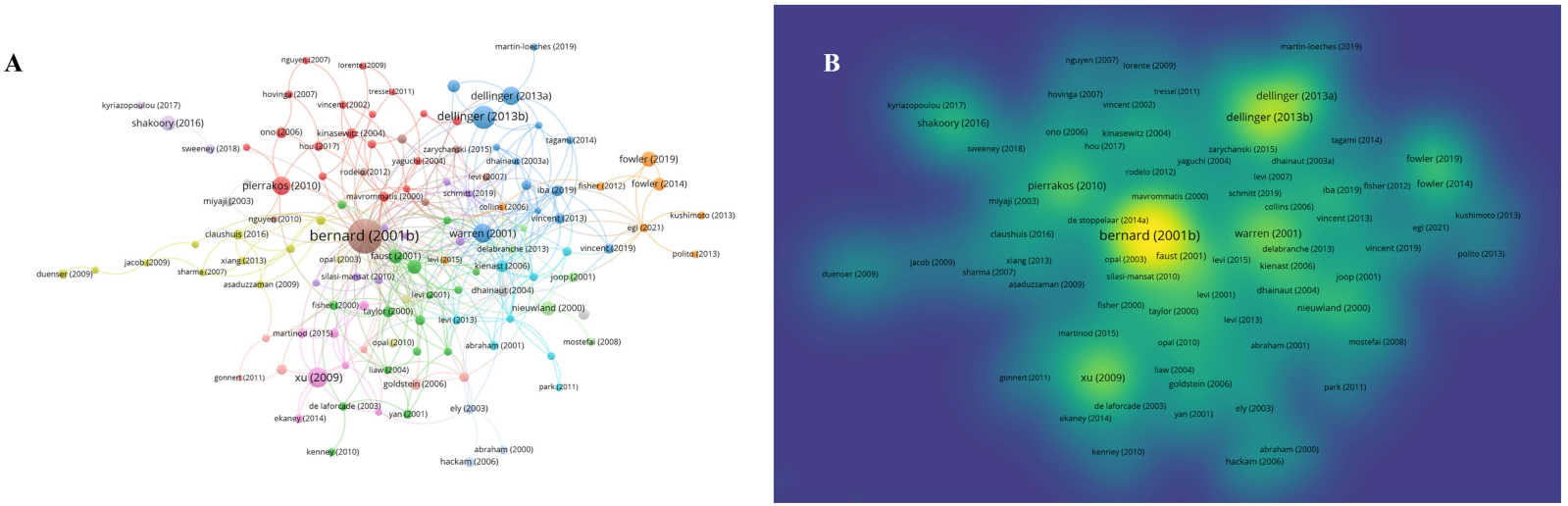

Figure 8 Co-citation analysis of foundational documents in sepsis and coagulation dysfunction research. (**A**) The document co-citation network map. Each node represents a cited document, with the node size proportional to its co-citation frequency. The links (edges) between nodes indicate that the two documents have been co-cited, with thicker lines representing stronger co-citation links. Node colors represent different clusters of closely related documents as identified by the CiteSpace clustering algorithm. (**B**) The document co-citation density map. The color intensity indicates the concentration of highly co-cited documents, with warmer colors (red) representing the core intellectual cornerstones of the field.

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Table 4 Top 10 Most Co-Cited Documents in the Field of Sepsis and Coagulation Dysfunction Research

Rank	First Author	Year	Title	Source	Citations
1	Bernard, GR	2001	Efficacy and safety of recombinant human activated protein c for severe sepsis	New Engl J Med (New England Journal of Medicine)	4188
2	Dellinger, RP	2013	Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012	Intensive Care Med (Intensive Care Medicine)	1609
3	Xu, Jun	2009	Extracellular histones are major mediators of death in sepsis	Nature Med (Nature Medicine)	1192
4	Warren, BL	2001	High-dose a randomized antithrombin III in severe sepsis: a randomized controlled trial	JAMA-J Am Med Assoc (Journal of the American Medical Association)	983
5	Dellinger, RP	2013	Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012	Crit Care Med (Critical Care Medicine)	962
6	Pierrakos, Charalampos	2010	Sepsis biomarkers: a review	Crit Care (Critical Care)	927
7	Shakoory, Bita	2016	Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior Phase III trial	Crit Care Med (Critical Care Medicine)	628
8	Fowler, Alpha A.	2019	Effect of vitamin c infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the citris-ali randomized clinical trial	JAMA-J Am Med Assoc (Journal of the American Medical Association)	593
9	Nieuwland, R	2000	Cellular origin and procoagulant properties of microparticles in meningococcal sepsis	Blood	507
10	Faust, SN	2001	Dysfunction of endothelial protein c activation in severe meningococcal sepsis	New Engl J Med (New England Journal of Medicine)	505

The largest and most central clusters, such as #0 "platelet function" and #1 "intravascular coagulation", represent the foundational pillars of the field, focusing on core hematological processes. The emergence of #3 "sepsis-induced coagulopathy" signifies the crucial conceptual shift towards a more specific clinical entity. More importantly, the map reveals the rise of highly specific, mechanism-driven research frontiers. The presence of distinct clusters like #6 "endothelial glycocalyx" and #8 "von willebrand factor" provides clear, data-driven evidence that the research focus is

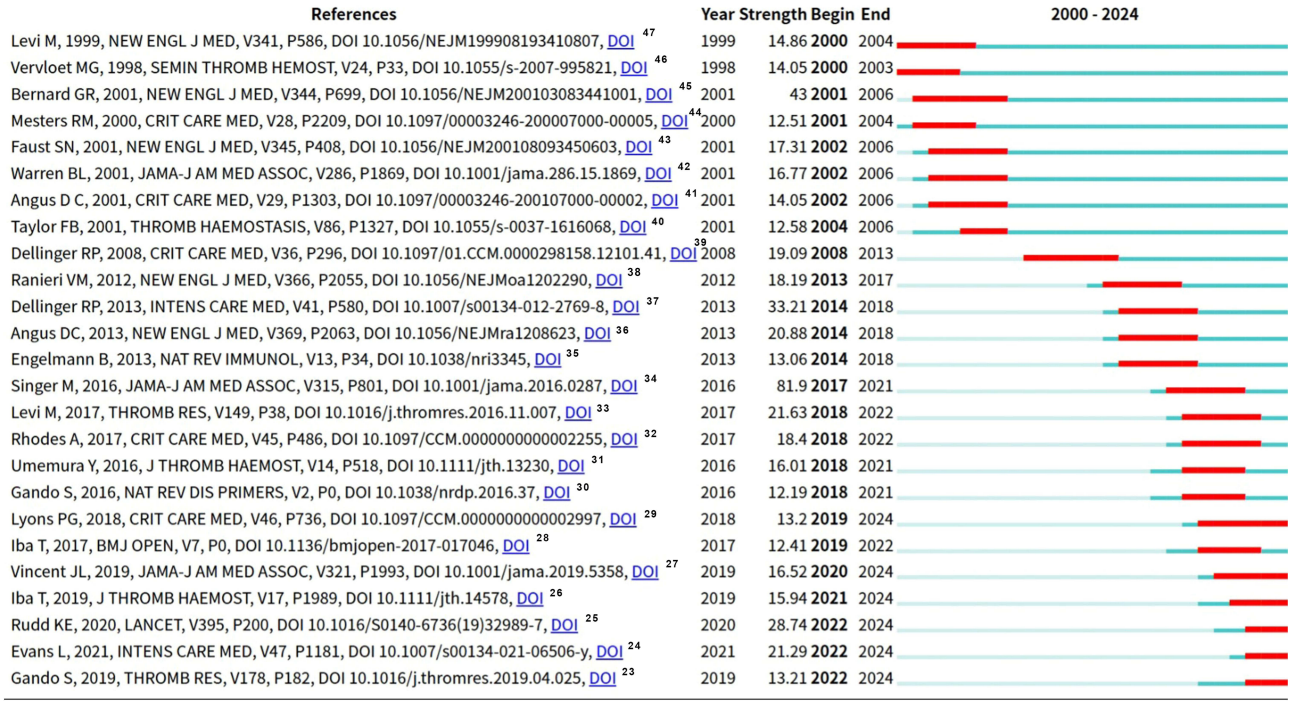


Figure 9 Top 25 documents with the strongest citation bursts in the field of sepsis and coagulation dysfunction research. This chart identifies foundational literature that experienced significant surges in citation frequency during specific periods. The red bar indicates the duration of each document's citation burst.

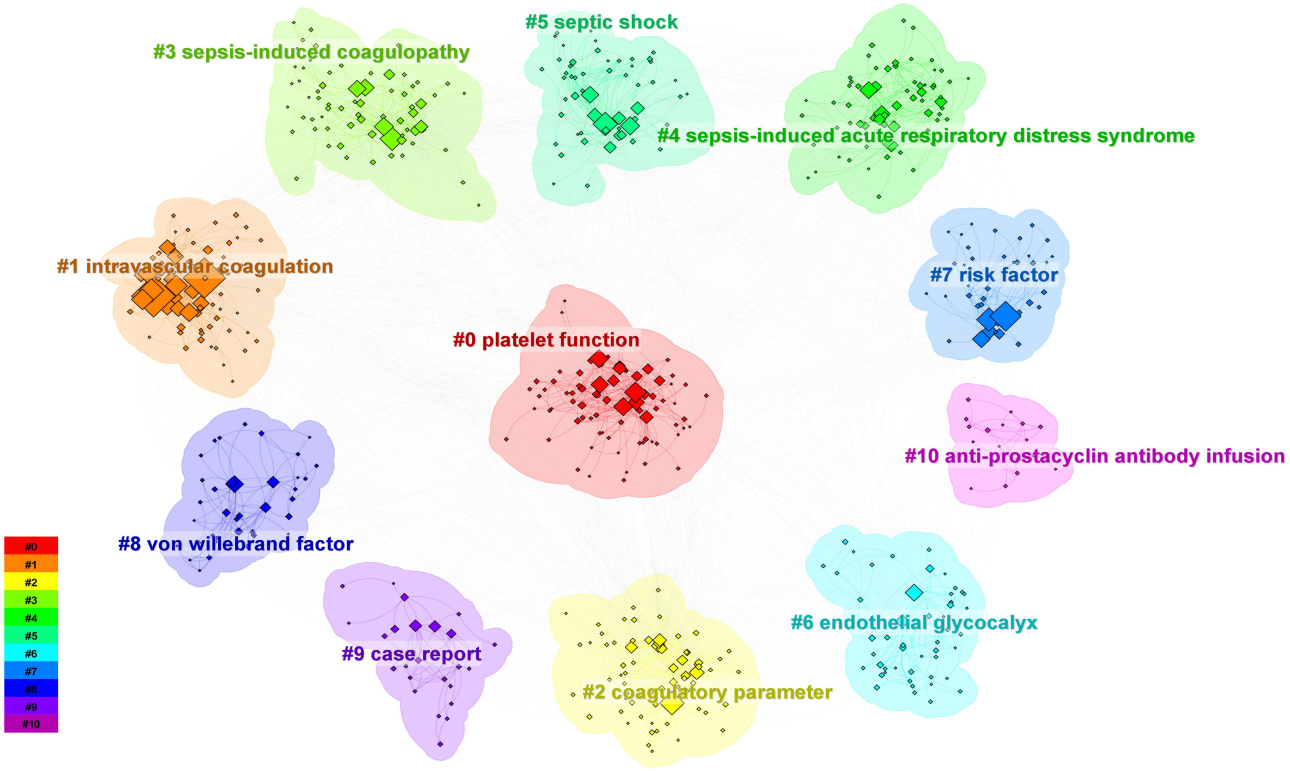


Figure 10 Keyword clustering map in the field of sepsis and coagulation dysfunction research. This map illustrates the main research themes in the field. Each colored region represents a distinct thematic cluster, which was identified by the CiteSpace clustering algorithm and subsequently assigned a meaningful academic label based on a manual review of its constituent keywords.

progressively moving from the systemic level of coagulopathy down to the molecular and cellular mechanisms occurring at the vascular interface.

Core Research Themes

The keyword co-occurrence network (Figure 11) reveals four main research pillars in this field: (1) Clinical Characteristics, Diagnosis, and Prognosis (Red Cluster); (2) Pathophysiological Mechanisms of Sepsis and Inflammation (Green Cluster); (3) Coagulation System Components and Endothelial Function (Blue Cluster); and (4) DIC, Shock, and Anticoagulant Therapy (Yellow Cluster). These four themes collectively delineate a complete research loop, starting from clinical problems, delving into basic mechanisms, and ultimately returning to therapeutic management. As evidenced by Table 5, beyond the core subject terms "sepsis" (918 occurrences, Total Link Strength [TLS]: 4379), "septic shock" (483, TLS: 2665), and "disseminated intravascular coagulation" (473, TLS: 2798), which exhibit exceptionally high frequencies and strong network connectivity, other high-frequency keywords also show significant prominence. These include "mortality" (346, TLS: 1931), "inflammation" (237, TLS: 1384), "management" (151, TLS: 779), and "critically ill patients" (144, TLS: 947). With average publication years concentrated between 2013 and 2018, these keywords reflect sustained high-level attention during this period. Collectively, these high-frequency and highly connected keywords form the core intellectual framework of the field, covering multiple facets such as disease states, critical complications, pathophysiological processes, clinical management, and prognosis.

Dynamic Evolution of Research Frontiers

The timeline view of keyword clusters and the analysis of burst keywords, presented together in Figure 12, provide a dynamic chronicle of the field's evolving research frontiers.

The timeline view (Figure 12A) visually maps the lifespan and prominence of the major research themes. It confirms that foundational topics such as #1 "intravascular coagulation" appeared early and have persisted. In contrast, highly

https://doi.org/10.2147/JMDH.S547136

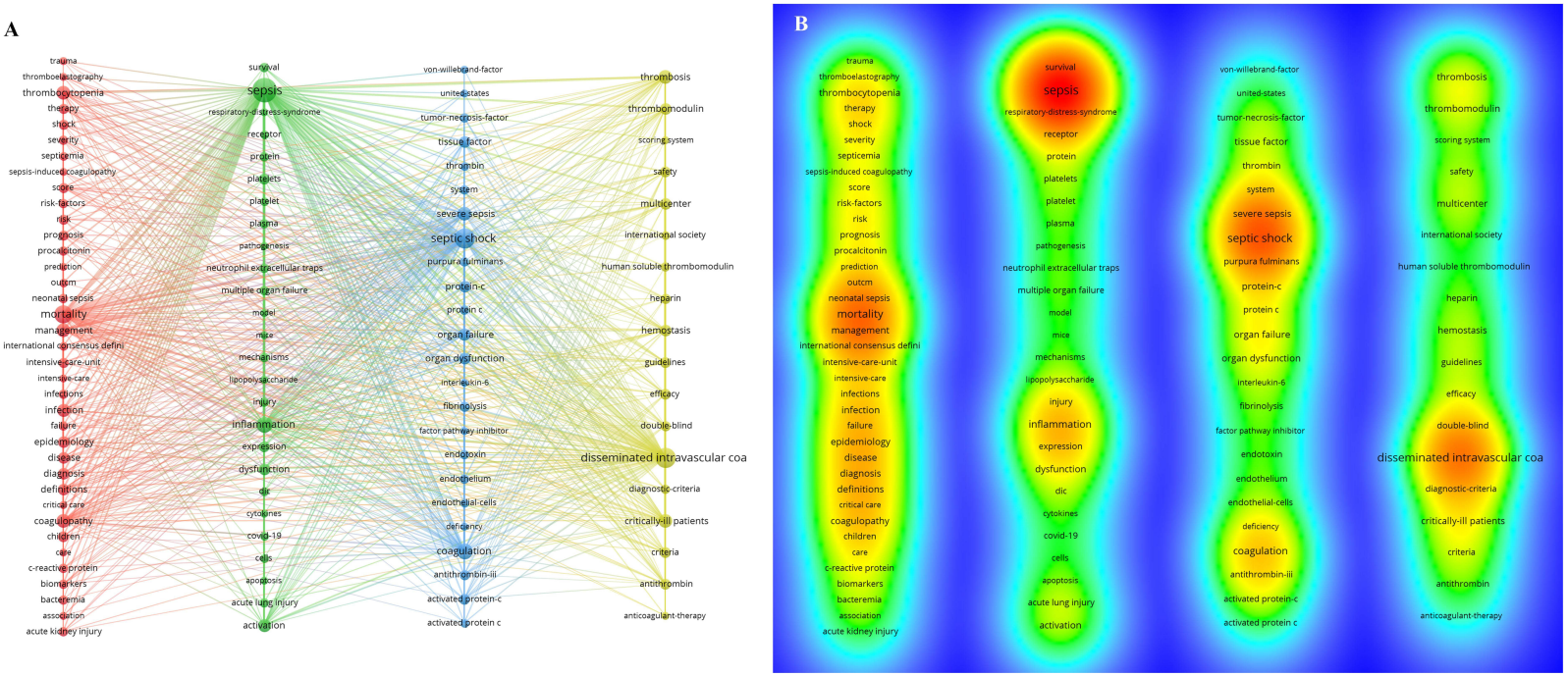


Figure 11 Co-occurrence analysis of high-frequency keywords in sepsis and coagulation dysfunction research. (**A**) Keyword co-occurrence network map. Each node represents a keyword, with its size indicating its frequency of occurrence. The links represent co-occurrence relationships, and different colors distinguish the four major thematic clusters identified by VOSviewer. (**B**) Keyword density map. The color intensity indicates the concentration of keywords, with warmer colors (eg, yellow, red) representing high-density areas, which signify the core research hotspots.

Table 5 Top 20 High-Frequency Keywords in the Field of Sepsis and Coagulation Dysfunction Research

Rank	Keyword	Occurrences	Total Link Strength	Avg. Pub. Year
1	Sepsis	918	4379	2016.55
2	Septic shock	483	2665	2014.77
3	Disseminated intravascular coagulation	473	2798	2014.22
4	Mortality	346	1931	2018.06
5	Inflammation	237	1384	2015.59
6	Coagulation	232	1342	2014.50
7	Management	151	779	2017.32
8	Coagulopathy	150	879	2017.95
9	Severe sepsis	150	863	2014.19
10	Critically ill patients	144	947	2016.85
11	Infection	129	585	2014.95
12	Activation	122	695	2015.37
13	Diagnosis	93	405	2017.08
14	Endothelial dysfunction	83	444	2015.90
15	Expression	74	378	2015.72
16	Children	67	279	2013.79
17	Risk	65	290	2016.08
18	Therapy	64	310	2015.38
19	Shock	53	309	2013.77
20	Acute lung injury	52	265	2016.85

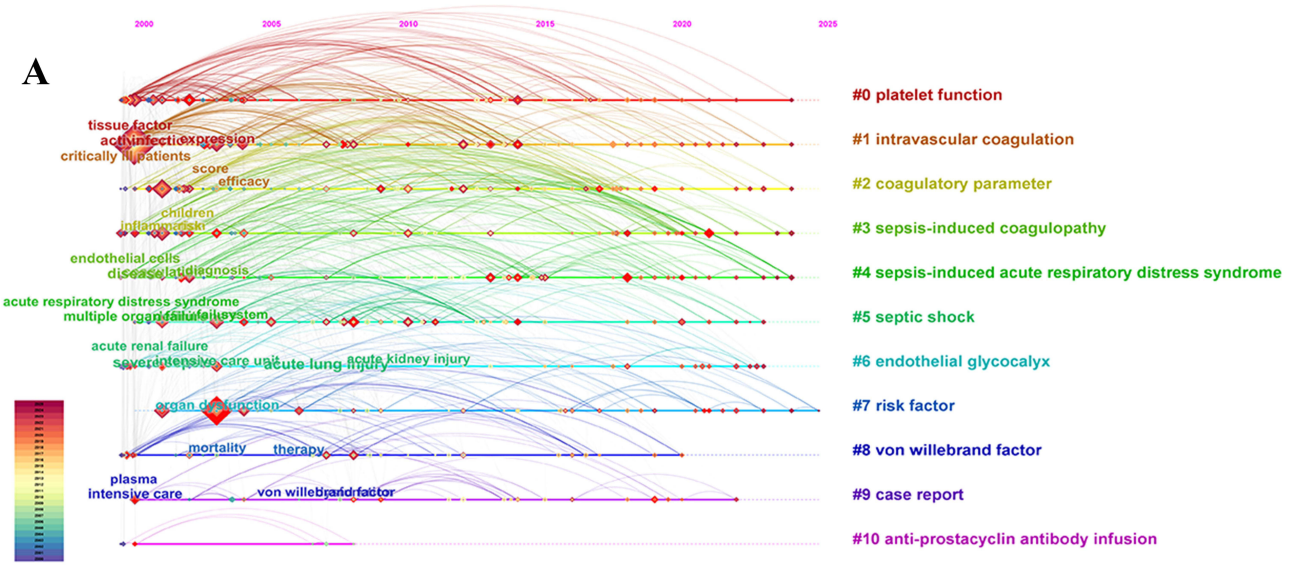
specific, mechanism-focused clusters like #6 “endothelial glycocalyx” are clearly shown to have emerged as significant research topics only in more recent years, powerfully illustrating the intellectual progression from broader clinical descriptions to deeper molecular investigations.

This macroscopic trend is substantiated by the burst keyword analysis (Figure 12B). The most significant paradigm shift captured is the conceptual evolution from “DIC” to “SIC”, where the keyword “sepsis-induced coagulopathy” exhibits a powerful and recent burst (strength 10.09). This quantifies the academic community’s pivot towards this more specific entity. Furthermore, early burst keywords like “protein c” and “tissue factor pathway inhibitor” reflect initial explorations into single anticoagulant targets. In contrast, more recent bursts, such as “neutrophil extracellular traps”, “diagnosis”, and “risk factors”, highlight the current research frontiers: a focus on the intricate mechanisms of immunothrombosis and the urgent clinical need for precise risk stratification and diagnostics.

Disciplinary Landscape: A Translational Medicine Ecosystem

The study of sepsis and coagulation dysfunction is inherently multidisciplinary, a fact substantiated by the distribution of publications across various Web of Science subject categories (Table 6). “General & Internal Medicine” emerges as the most prolific research area (611 articles, 33.19%), reflecting the systemic nature of sepsis and its primary management within this domain. It is closely followed by “Hematology” (355 articles, 19.28%), which forms the core scientific foundation for understanding coagulation.

However, an analysis of citation impact reveals a deeper narrative. Foundational basic science disciplines, despite having fewer publications, demonstrate exceptionally high average citations, such as “Research & Experimental Medicine” (42.69 average citations) and “Immunology” (38.58 average citations). This indicates that fundamental research in these areas provides the crucial mechanistic insights that are highly valued and cited by the broader community. Notably, “Critical Care Medicine”, while appearing as a more focused category, boasts the highest average citation rate by a significant margin (81.69), underscoring its role in publishing landmark clinical trials and guidelines that shape clinical practice. This quantitative evidence paints a clear picture of a translational medicine ecosystem: the field is driven by clinical problems encountered in internal and critical care medicine, built upon the core knowledge



B

Keywords	Year	Strength	Begin	End	2000 - 2024
protein c	2000	22.8	2000	2009	
tumor necrosis factor	2000	19.04	2000	2005	
escherichia coli	2000	9.85	2000	2006	
tissue factor pathway inhibitor	2000	4.65	2000	2002	
activated protein c	2000	23.5	2001	2012	
necrosis factor alpha	2001	4.27	2001	2004	
organ failure	2000	6.29	2006	2008	
children	2002	4.41	2007	2011	
organ dysfunction	2003	6.05	2011	2016	
impact	2014	4.48	2014	2016	
multicenter	2000	5.06	2015	2018	
neutrophil extracellular traps	2014	5.07	2017	2018	
international consensus definitions	2018	6.26	2018	2021	
anticoagulant therapy	2018	6.17	2018	2019	
diagnostic criteria	2013	5.24	2018	2020	
platelets	2017	5.63	2019	2022	
management	2001	5.32	2019	2020	
criteria	2013	5.11	2020	2021	
sepsis-induced coagulopathy	2021	10.09	2021	2024	
outcm	2014	8.57	2021	2024	
thrombocytopenia	2002	5.85	2021	2024	
mortality	2003	5.42	2021	2022	
prevalence	2021	4.78	2021	2024	
risk factors	2008	4.77	2022	2024	
diagnosis	2003	4.38	2022	2024	

Figure 12 Dynamic Evolution of Research Frontiers in Sepsis and Coagulation Dysfunction. (**A**) Timeline view of keyword clusters. This map shows the evolution of major research themes over time. Each horizontal line represents a research theme (cluster), and the circles on the lines are specific keywords, with their position indicating their first appearance year and their size representing their frequency. (**B**) Top 25 keywords with the strongest citation bursts. This chart identifies keywords that rapidly gained popularity in specific periods. The red bar indicates the duration of each keyword's burst, and the "Strength" value measures the intensity of this growth in popularity.

Table 6 Top 10 Main Research Directions (Based on Web of Science Subject Categories) in the Field of Sepsis and Coagulation Dysfunction Research

Rank	Research Interests	Documents	Percentage	Total Citations	Average Citations
1	General & Internal Medicine	611	33.19%	15,432	25.26
2	Hematology	355	19.28%	9,875	27.82
3	Cardiovascular System & Cardiology	220	11.95%	7,109	32.31
4	Pediatrics	121	6.57%	3,541	29.26
5	Surgery	119	6.46%	2,890	24.29
6	Immunology	104	5.65%	4,012	38.58
7	Infectious Diseases	96	5.21%	3,118	32.48
8	Pharmacology & Pharmacy	76	4.13%	2,557	33.64
9	Research & Experimental Medicine	70	3.80%	2,988	42.69
10	Science & Technology - Other Topics	69	3.75%	5,310	81.69

from hematology, and continuously fueled by high-impact discoveries from basic immunology and experimental research.

Discussion

To our knowledge, this is the first study to employ bibliometric methods, in conjunction with visualization tools such as VOSviewer and CiteSpace, to conduct a comprehensive and systematic analysis of the 1,715 English-language articles on sepsis and coagulation dysfunction indexed in the Web of Science Core Collection (SCIE database) from 2000 to 2024. Through an in-depth analysis of annual publication trends, major contributing countries/regions, prolific and co-cited authors, representative journals, key cited documents, keyword networks, and interdisciplinary collaborations, this study not only delineates the developmental trajectory and panoramic knowledge structure of the field over more than two decades but also reveals current research hotspots, evolutionary pathways, and potential future frontiers.

General Overview and Global Landscape

Over the past two decades, the global research on sepsis-associated coagulopathy has demonstrated significant and sustained growth, especially with an accelerated increase in annual publication volume since 2020 (Figure 2). This robust growth curve not only quantifies the field's increasing prominence in global clinical medicine but also reflects that as our understanding of sepsis pathophysiology deepens, coagulopathy, as a central and life-threatening complication, has become a focal point of intense interest for the global scientific community.[46,47]

Our analysis unveils a research landscape predominantly led by developed nations, with emerging scientific powers rapidly ascending. The United States plays an undisputed central role in both knowledge production and agenda-setting within this domain. Its dual leadership in publication volume and total citations testifies to its robust research infrastructure and enduring academic influence (Table 1 and Figure 3). China and Japan, following closely, constitute the core of Asia's research force. Notably, however, the relatively low average citations per paper for Chinese publications suggests significant potential for enhancing the international impact and translational value of its research output. The international collaboration network (Figure 4) further corroborates that while a US-centric global cooperation network has indeed formed, the most efficient knowledge exchange occurs primarily within North America, Western Europe, and East Asia. Fostering broader and more profound North-South collaborations will be crucial for accelerating global progress in this field.

The Impact of the COVID-19 Pandemic on the Research Landscape

A critical observation from our analysis is the sharp increase in publications after 2020, a trend that warrants careful interpretation. This surge is inextricably linked to the COVID-19 pandemic. Severe COVID-19 presented as a unique and widespread model of viral sepsis, characterized by severe thromboinflammation, endothelial dysfunction, and coagulopathy. Consequently, a vast body of research on COVID-19-associated coagulopathy (CAC) was produced, much of

which directly built upon or contributed to the existing knowledge base of SIC. While this influx of research has profoundly enriched our understanding of immunothrombosis, it is crucial to acknowledge that this surge may not represent a sustainable, organic growth rate for the broader field of sepsis research. It reflects a massive, concentrated research effort in response to a global crisis, and the long-term trajectory of the field may differ as the focus on pandemic-specific research subsides.

Interpretation of Core Hotspots and Evolution of the Knowledge Base

Through an in-depth analysis of keyword and co-citation networks, we have not only identified research hotspots but, more importantly, have observed the evolution of the underlying knowledge base and conceptual paradigms.

From DIC to SIC: Conceptual Refinement and Diagnostic Evolution

"Disseminated intravascular coagulation (DIC)" and "sepsis-induced coagulopathy (SIC)" are undoubtedly the most central topics in this domain. Our analysis clearly demonstrates a significant conceptual evolution: the research focus is converging from the relatively broad concept of DIC to a more specific pathophysiological entity—SIC.[17,48] The strong burst of the keyword "sepsis-induced coagulopathy" (Figure 12B) is a data-driven manifestation of this trend. The essence of this shift lies in a deeper understanding of the unique pathophysiology of sepsis-associated coagulopathy (ie, thromboinflammation characterized by fibrinolysis shutdown).[49,50] This, in turn, has driven the development and validation of diagnostic tools, such as the ISTH SIC score, aimed at the earlier and more precise identification of high-risk patients.[26,51]

Thromboinflammation: An Integrative Core Pathological Theory

A central finding of our analysis is the convergence of high-frequency keywords around the concept of thromboinflammation, which stands as the integrative core pathological theory of this domain. As revealed in our keyword analysis (Table 5 and Figure 11), terms central to the inflammatory response, such as "inflammation", "cytokines", and "activation", are inextricably linked with the vocabulary of hemostasis, including "coagulation" and "thrombosis." This data-driven observation reinforces the theory that coagulation activation is not a mere secondary phenomenon to inflammation but an intrinsic component of the host's innate immune response.[52] The literature suggests this is driven by an uncontrolled inflammatory cascade triggered by infection, where mechanisms such as cytokine storms,[53–55] the formation of NETs,[56,57] and the release of DAMPs (eg, extracellular histones)[58,59] collectively drive the pathological activation of the coagulation system, locking it in a self-amplifying vicious cycle.

Vascular Endothelium: The Center Stage of Thromboinflammation

The emergence of keyword cluster #6, "endothelial glycocalyx" (Figure 10), as a distinct and prominent research theme provides clear data-driven support for this focus. It quantitatively confirms that the academic community's attention is decisively shifting towards the vascular endothelium as the "center stage" of thromboinflammation. In sepsis, endothelial cells undergo a catastrophic phenotypic switch from an anticoagulant to a procoagulant state, hallmarked by events such as the degradation and shedding of the protective glycocalyx.[60–62] Endothelial injury and dysfunction are not merely a consequence of the coagulation storm but also its critical amplifier and driver, directly leading to microcirculatory failure and multiple organ dysfunction.

Research Frontiers and Future Trends

Based on the preceding analysis of research hotspots and the knowledge base, combined with keyword evolution trends (Figure 12A) and burst strength (Figure 12B), we predict that future research in sepsis and coagulation dysfunction will focus on the following frontiers:

i. **Molecular Phenotyping and Precision Intervention for SIC**: As indicated by our keyword burst analysis (Figure 12B), the strong emergence of "sepsis-induced coagulopathy" in recent years directly reflects a paradigm shift from broad DIC research to more precise SIC subtyping. Future studies will likely leverage multi-omics technologies (genomics, proteomics, metabolomics) to identify SIC subtypes with distinct pathophysiological

drivers (eg, the "hypocoagulable" phenotype[63]) and to develop targeted therapeutic strategies for these specific subtypes. Such precision stratification holds the promise of overcoming the inconclusive outcomes of past broad-spectrum anticoagulant trials and is a critical step toward achieving personalized therapy in sepsis.[64,65]

ii. **Dissecting the Cellular and Molecular Interaction Network of the Thromboinflammatory Microenvironment**: The recent burst of "neutrophil extracellular traps" (Figure 12B) and the formation of central clusters around #0 "platelet function" and #8 "von willebrand factor" (Figure 10) highlight a clear move towards understanding the intricate cellular crosstalk in the thromboinflammatory microenvironment. Future research will likely delve deeper into the intricate regulatory networks of Extracellular Vesicles/Microparticles (EVs/MPs) in mediating procoagulant and proinflammatory signals between cells.[58,66,67] Elucidating this micro-environmental signaling crosstalk may unveil new therapeutic targets, such as targeting EVs to interrupt the transmission of pathological information.[68,69]

iii. **Endothelial Protection and Repair Strategies**: Our identification of #6 "endothelial glycocalyx" (Figure 10) as an emerging research cluster provides strong, data-driven support for predicting that endothelial protection will become a key future research frontier. Given the central role of endothelial injury, developing drugs and therapeutic strategies aimed at preserving the integrity of the endothelial barrier and restoring glycocalyx function represents a highly promising research avenue.[70,71] For instance, drugs like Sulodexide have shown potential for clinical translation by demonstrating an ability to remodel the glycocalyx and improve vascular permeability.[60–62]

iv. **Innovations in Coagulation Monitoring and Point-of-Care Application**: Keyword cluster #2, "coagulatory parameter", (Figure 10) which encompasses terms related to viscoelastic tests, highlights the growing emphasis on holistic coagulation assessment. Future research will focus on advancing the application of point-of-care testing (POCT) technologies, such as thromboelastography (TEG/ROTEM), to guide individualized anticoagulation and transfusion strategies, thereby enabling more precise, real-time coagulation management.[72,73] This is crucial for rapidly identifying hypercoagulable or fibrinolysis-shutdown states and making timely therapeutic adjustments.

v. **Application of Artificial Intelligence (AI) and Machine Learning**: As demonstrated in many medical fields,[74] the integration of AI is a significant trend. In the SIC domain, a key future direction will be the development of machine learning-based dynamic risk prediction models. These models will integrate clinical, multi-omics, and continuous monitoring data to provide early warnings and precise risk stratification for the onset and progression of SIC.[75,76] This approach aims to address the challenge of managing the multidimensional, high-volume data increasingly generated in critical care, translating complex data patterns into clinically actionable decision support.

Strengths and Limitations

To our knowledge, this is the first study to apply bibliometric and knowledge mapping visualization methods to the global research on sepsis and coagulation dysfunction, providing a macroscopic knowledge landscape and developmental trajectory for researchers in this field.

However, this study has several inherent limitations. First, the data were sourced exclusively from the SCIE database of WoSCC, potentially omitting relevant literature indexed in other databases (eg, PubMed, Scopus). Second, this study included only English-language publications, which may introduce a language bias. Third, bibliometric analysis is primarily based on the external characteristics of publications (such as citations and keywords) and cannot provide an in-depth evaluation of the intrinsic academic quality or methodological rigor of the individual studies. Finally, due to the inherent time lag in citations, the most recent research findings may not be fully reflected in the co-citation analysis, potentially affecting a comprehensive capture of the very latest frontiers.

Conclusion

This study systematically reveals the panoramic research landscape of sepsis and coagulation dysfunction over the past two decades. More centrally, this research delineates a profound evolution in the field's paradigms, shifting from early

explorations of macroscopic syndromes like Disseminated Intravascular Coagulation (DIC) towards the refined diagnosis of Sepsis-Induced Coagulopathy (SIC) and, more recently, into the intricate, mechanism-driven frontiers of thromboinflammation, such as the roles of Neutrophil Extracellular Traps (NETs) and the endothelial glycocalyx.

This evolution signifies a deeper scientific understanding that converges on the complex regulatory networks centered on thromboinflammation, where emerging frontiers such as Neutrophil Extracellular Traps (NETs) and the endothelial glycocalyx have become prominent research hotspots. The academic blueprint constructed by this analysis is a quantitative summary of past research, offering a structured reference for the scientific community. For researchers, it highlights established knowledge domains and areas of intense recent activity, which may help in identifying research gaps. For clinicians, the analysis reflects a clear trend in the literature away from generalized approaches and towards personalized coagulation management.

Ultimately, the macroscopic perspective provided by this study represents a systematic summarization of two decades of academic achievement. By identifying the foundational literature, core knowledge clusters, and the evolution of research hotspots, this work provides a valuable, data-driven reference for researchers to grasp the field's dynamics and can inform the design of future studies, with the goal of improving outcomes for sepsis patients worldwide.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author, Bangjiang Fang.

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Certain data included herein are derived from Clarivate (Web of Science). All rights reserved.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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