

Research trends and hotspots in sepsis-induced coagulopathy during 1995–2024: a 30-year bibliometric analysis

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Abstract

Background: Sepsis-induced coagulopathy (SIC) is a life-threatening complication of sepsis characterized by dysregulated coagulation, hyperinflammation, and microvascular thrombosis. Despite advancements in its pathophysiology, therapeutic strategies remain controversial, and clinical trials have yielded inconsistent outcomes.

Methods: This study conducts a bibliometric analysis (1995–2024) to map research trends, identify knowledge gaps, and evaluate the translational challenges in SIC management. A systematic search of the Web of Science Core Collection (6382 articles) and Scopus (8423 articles) retrieved on sepsis-related coagulation dysfunction. VOSviewer and Bibliometrix analyzed publication trends, citation networks, international collaborations, and keyword co-occurrence. Metrics included annual growth rates, total link strength, and relative research interest. We visualized temporal and thematic trends to highlight emerging frontiers and interdisciplinary linkages.

Results: Global research output exhibited exponential growth (annual rate: 18.4%), peaking during the coronavirus disease 2019 pandemic. The United States and China dominated research contributions, with the University of Texas MD Anderson Cancer Center leading in citation impact. Van Der Poll, Tom (Netherlands), and Toshiaki Iba (Japan) emerged as pivotal figures, focusing on molecular mechanisms and diagnostic standardization, respectively. Keyword clustering revealed 4 pillars: (1) etiology and clinical management, (2) molecular mechanisms, (3) biomarkers and prognostics, and (4) pathophysiology and syndromes. Coronavirus disease 2019–associated coagulopathy and artificial intelligence–driven diagnostics emerged as recent hotspots.

Conclusions: This analysis reveals the exponential but heterogeneous expansion of SIC research, driven by mechanistic discoveries and pandemic-related demands. Persistent challenges include the standardization of diagnostic criteria, patient heterogeneity in clinical trials, and geographic disparities in research capacity. Future priorities include integrating precision medicine and adopting artificial intelligence for patient stratification. Bridging mechanistic insights with clinical translation will be critical to improving outcomes in SIC.

Keywords: Bibliometric analysis, COVID-19, Immunothrombosis, Sepsis-induced coagulopathy, Visualization, VOSviewer

Introduction

Sepsis, a systemic inflammatory syndrome precipitated by dysregulated host responses to infection, represents a critical global health burden characterized by high morbidity and mortality.^[1]

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The datasets generated during and/or analyzed during the current study are publicly available.

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Central to its pathophysiology is the interplay between hyperinflammation, immune dysregulation, and hemostatic imbalance, with sepsis-induced coagulopathy (SIC) emerging as a pivotal contributor to multiorgan failure and adverse clinical outcomes.^[2, 3] The term SIC was introduced by the International Society on Thrombosis and Haemostasis (ISTH) in 2017.^[4] It serves to identify sepsis patients in the early stages of coagulopathy before the development of overt disseminated intravascular coagulopathy (DIC), marking a significant progression from the traditional DIC diagnostic criteria.

The pathophysiology of SIC is characterized by a complex, self-amplifying interplay among systemic inflammation, immune activation, and the coagulation system.^[5] The initial hyperinflammatory response, driven by innate immune cells (monocytes/macrophages), detects damage-associated molecular patterns, leading to the excessive release of proinflammatory cytokines and tissue factor, which directly activates the cycle of inflammation and coagulation cascade.^[6] A pivotal mechanism in this process is immunothrombosis, primarily facilitated by neutrophil extracellular traps (NETs), which promotes microvascular thrombosis.^[7] This is compounded by endothelial injury and glycocalyx shedding,^[8] which expose subendothelial procoagulant surfaces, trigger the intrinsic pathway, and release factors such as von Willebrand factor (vWF)^[9] while simultaneously suppressing fibrinolysis through plasminogen activator inhibitor-1.^[10] Furthermore, platelets are directly and indirectly activated, contributing to thrombocytopenia and facilitating the formation of

microthrombi.^[11] While the formation of new thrombi can help localize and hinder the spread of infection, this beneficial effect is counterbalanced by a detrimental paradox: the resulting microcirculatory dysfunction exacerbates organ ischemia, ultimately contributing to organ failure.^[12]

To early detect SIC and facilitate the management of coagulopathy in sepsis, 2 definitions and scoring criteria for SIC were established by the ISTH and the Japanese Association for Acute Medicine, respectively.^[4, 13] The diagnostic criteria for SIC have evolved from those established for overt DIC to enable earlier identification and enhance specificity in the context of heterogeneous sepsis populations.^[14] Clinical evidence underscores its prognostic significance, with sepsis-associated DIC correlating with mortality rates exceeding 40%, highlighting the urgency of targeted interventions.^[13, 15, 16] However, these criteria remain relatively complex, and their prognostic accuracy and clinical utility require further validation in additional studies.^[17]

Despite decades of research, therapeutic strategies for SIC remain contentious. Anticoagulant therapies, including recombinant activated protein C,^[18] antithrombin,^[19] recombinant tissue factor pathway inhibitor,^[20] and recombinant thrombomodulin (rTM),^[21] have yielded inconsistent outcomes in clinical trials, hindered by heterogeneous patient populations, suboptimal dosing regimens, and delayed intervention.^[22] Although rTM has been extensively used in Japan for the treatment of DIC, a recent randomized controlled trial (SCARLET) failed to demonstrate its effectiveness in reducing 28-day all-cause mortality.^[23] Furthermore, current guidelines lack consensus on standardized management protocols.^[24, 25] The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 recommend antithrombin or rTM for the treatment of SIC.^[25] The ISTH states that the evidence for anticoagulant therapy in patients with SIC remains inadequate.^[14] Notably, the surviving sepsis campaign guidelines^[24] focus primarily on venous thromboembolism (VTE) prophylaxis rather than providing specific therapeutic recommendations for SIC patients.

In summary, despite significant advancements in our understanding of SIC, ranging from its conceptual definition and pathophysiological mechanisms to diagnostic and therapeutic strategies, a genuinely effective and targeted solution remains elusive. The existing literature is highly fragmented, while narrative reviews are often subjective and lack quantitative integration. Furthermore, the exponential growth of related literature makes it increasingly challenging for both clinicians and researchers to stay current with developments and identify genuine frontiers in the field. This situation highlights the crucial need to map the intellectual landscape of SIC research objectively. A systematic analysis is indispensable for delineating its core knowledge structure and identifying evolving trends, thereby providing a valuable reference and guiding future investigative directions.

This bibliometric analysis systematically maps the evolving landscape of SIC research, synthesizing advancements in pathogenesis, diagnostic criteria, and therapeutic innovations between 1995 and 2024. By analyzing quantitative metrics and qualitative insights, we identify emerging trends, persistent knowledge gaps, and interdisciplinary collaborations that are shaping the field. Furthermore, we critically evaluate the translational challenges of anticoagulant therapies, offering evidence-based perspectives to refine clinical trial design and therapeutic paradigms. Ultimately, this work aims to catalyze future research by providing a scaffold for hypothesis-driven investigations and personalized management strategies in SIC.

Materials and methods

Data retrieval, search strategy, and processing workflow

The Web of Science Core Collection was systematically searched for English-language articles on sepsis-related coagulation dysfunction from January 1, 1995, to December 31, 2024. The literature search was completed on a single day (October 11, 2025) to prevent citation fluctuations caused by rapid publication updates. The search strategy (Supplementary File 1, <https://links.lww.com/ECCM/A111>) was refined to reflect the evolving terminology from the early term “septicemia” to the established term “sepsis,” and “sepsis-associated coagulation dysfunction” to the now widely recognized concept of SIC. Publications were restricted to Articles. Data were exported in “plain text” format with the “Full Record and Cited References” option, providing 22 bibliographic fields including authors, abstracts, cited references, citation counts, keywords, funding information, and PubMed IDs.

To enhance comprehensiveness and ensure cross-database robustness, a parallel search was performed in Scopus using the same conceptual framework on the same day. The initial retrieval yielded 6382 records from Web of Science Core Collection and 8423 records from Scopus, resulting in a combined dataset of 14,805 records before deduplication.

All records were merged and underwent a multistep deduplication process using a hybrid matching algorithm based on DOI, article title, and first-author combinations. Following deduplication, 14,475 unique records remained. A subsequent language filter was applied to retain only English-language publications. According to the language filtering report, 14,467 records (99.9%) were written in English, while a small number of non-English records—including Portuguese (n = 3), German (n = 2), Italian (n = 2), and Spanish (n = 1)—were removed. For this bibliometric analysis, data from Mainland China, Hong Kong, Macao, and Taiwan were merged and are presented under the unified designation of “China” throughout the manuscript. The final dataset, comprising 14,467 English-language publications, served as the basis for all subsequent bibliometric and knowledge mapping analyses.

Bibliometric analysis and visualization

Two independent authors (Chen G and Song B) separately gathered information from all the incorporated publications. Statistical tables and annual publication trend charts were generated using Microsoft Office Excel 2019. Comprehensive bibliometric analyses and heatmap visualizations were conducted in the R-based package Bibliometrix (version 4.3.3, R Foundation for Statistical Computing, Vienna, Austria). Additionally, VOSviewer (version 1.6.20, Leiden University, Leiden, The Netherlands) and CiteSpace 6.2.R6 (Drexel University, Philadelphia, PA, USA) were used to construct and visualize knowledge maps across multiple dimensions, including countries/regions, institutions, authors, journals, keywords, and cited references. These tools collectively enabled a multilayered exploration of the structural, temporal, and intellectual landscapes of research on sepsis-related coagulation dysfunction. An overview of the bibliometric process is shown in Figure 1.

Results

Annual publication volume analysis

A total of 14,467 publications on the topic of SIC were retrieved from January 1, 1995, to December 31, 2024 (spanning 30 years). The annual publication trend (Fig. 2A) reveals a distinct

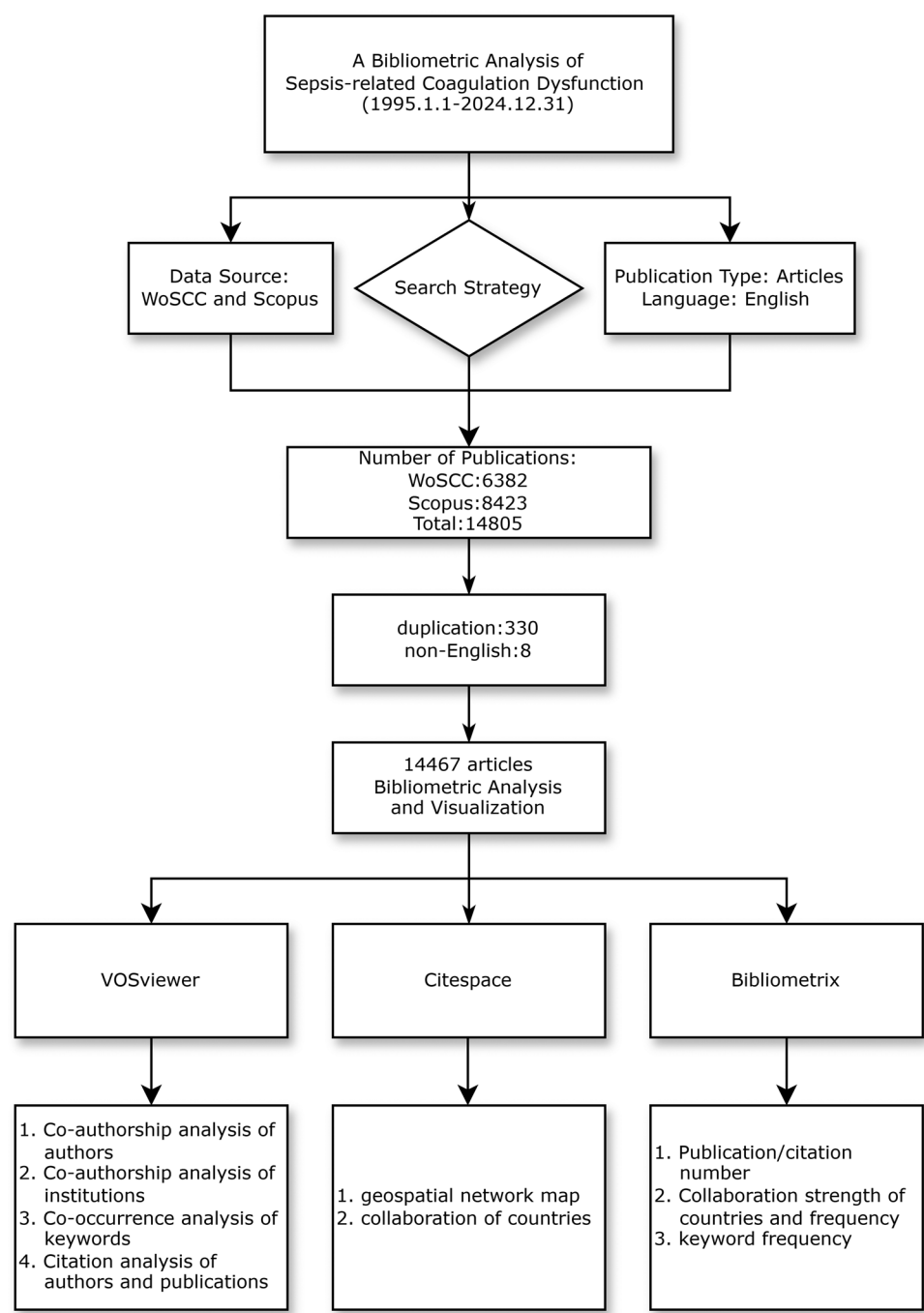


Figure 1. Workflow of the study.

exponential growth pattern ($y = 338.77e^{0.1397x}$, $R^2 = 0.9542$), indicating significant exponential growth in this field. A rapid growth phase reached a peak of 1275 publications in 2021, primarily driven by multicenter clinical studies and the coronavirus disease 2019 (COVID-19) pandemic. The trend confirms the field's establishment as a sustained international research priority.

Analysis of national publication volume and collaboration

National publication counts (Supplementary Table 1, <https://links.lww.com/ECCM/A112>) revealed that the United States was the leading contributor, ranking first in both total publications (5307 articles) and the overall total link strength (4814). Despite ranking 8th in publication volume, the Netherlands ranked first

in average citations per article (129.52). China ranked second in the quantity of publications (1274 articles) but lagged in average citations and international collaboration, suggesting a need to enhance research quality, global partnerships, and academic influence. Japan ranked third, but with a higher total number of citations. Collaborative efforts among nations further highlighted the leadership of the United States and Europe in advancing research quality within this domain (Fig. 2B).

Productivity and collaboration analysis of institutions and authors

The top 10 institutions by publication output are listed in Supplementary Figure 1, <https://links.lww.com/ECCM/A113>.

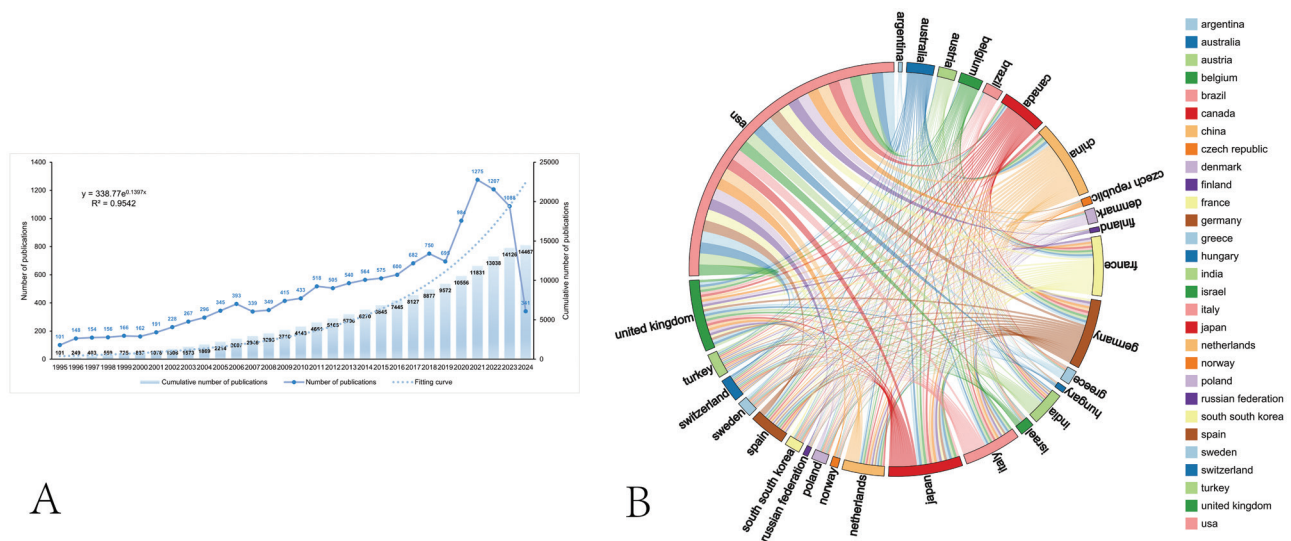


Figure 2. (A) Annual publication trends in sepsis-induced coagulopathy research, 1995–2024. The line graph illustrates the long-term evolution of publication output, reflecting the dynamic development of research intensity and scholarly attention in the field. An exponential growth model ($y = 338.77e^{0.1397x}$, $R^2 = 0.9542$) is fitted to the data, indicating a consistent and robust expansion over the 30 years. (B) Chord diagram of international research collaboration in sepsis-induced coagulopathy. This visualization illustrates the global collaborative network structure, where the width of the ribbons between countries corresponds to the intensity of collaboration. The chord diagram reveals both the density of research partnerships and the asymmetrical nature of international cooperation. Distinct collaborative clusters centered around major research economies are visible, illustrating a multipolar yet interconnected global research landscape.

The University of Texas MD Anderson Cancer Center has consistently demonstrated exceptional research output and impact, ranking first among institutions with 50,349 total citations across 203 publications. The University of Amsterdam ranked second with 179 publications and 14,711 citations (Supplementary Table 2, <https://links.lww.com/ECCM/A114>). This network visualization (Fig. 3A) delineates the global collaborative structure among major research institutions, with 3 distinct regional clusters emerging: North America, Europe, and East Asia. The high node density and thick connecting lines signify a highly active and interconnected research community in clinical, critical care, and coagulation studies.

Supplementary Figure 1, <https://links.lww.com/ECCM/A113>, also shows the top 10 authors in terms of publication volume, revealing a distinct geographical distribution, with Japan contributing 5 researchers, the Netherlands 2, and the United States 3. The top authors, Van Der Poll, Tom (Netherlands), rank first with 72 publications and 4553 citations. Following Iba, Toshiaki, and Gando, Satoshi, both from Japan, have published 61 articles with 3459 citations and 54 articles with 3341 citations. These individuals are pivotal figures in the field, whose work has exerted a profound influence on its development.

This co-authorship network map (Fig. 3B) delineates collaborative patterns among researchers. The right-side region, anchored by researchers such as Tom van der Poll, Marcel Levi, Satoshi Gando, and Toshiaki Iba, constitutes the network's core and represents a stable, long-standing central research community that focuses on inflammatory responses, coagulation pathophysiology, and the clinical management of DIC. The exceptionally high density of internal connections indicates a highly cohesive academic nucleus. Japanese scholars, including Mineji Hayakawa, Hiroshi Ogura, and Goichi Honda, form a distinct green aggregation zone within this region, collectively establishing a dual-core “East Asia-Europe/America” collaborative structure with their European and American counterparts. The large left-side cluster exhibits a clear oncology-oriented focus,

comprised of highly prolific clinical investigators such as Hagop Kantarjian, Guillermo Garcia-Manero, and Philippe Moreau. Their research primarily concentrates on chemotherapy-induced coagulopathy and cancer-associated thrombotic risk.

Citation analysis

This co-citation network (Fig. 3C) visualizes the evolutionary knowledge structure of highly cited publications, delineating citation pathways and intellectual origins across different time periods (the citation list is provided in Supplementary Table 3, <https://links.lww.com/ECCM/A115>). The node labeled “Bernard (2001)^[18]” appears as the most prominent node in the center-left region, serving as a cornerstone publication that established early mechanistic understanding of sepsis and DIC. It anchors a purple cluster comprising works such as “Marshall (2001)^[26]” and “Wong (2005)^[27]” collectively forming the theoretical foundation for early research on immune regulation and the crosstalk between inflammation and coagulation. Adjacent to this, a blue cluster featuring pivotal publications, such as “Levi (1999a,^[28] 1999b^[29])” demonstrates a high connection density, indicating their broad relevance across multiple research themes. These works represent fundamental studies in coagulation mechanisms, anticoagulant strategies, and pathological investigations. A green cluster focuses on clinical research from 1995 to 2005, including seminal epidemiological studies such as “Abraham (1998)^[30]” and “Rangel-Frausto (1995)^[31]” that established crucial references for sepsis disease management and clinical diagnosis. The yellow cluster, dominated by publications from 2006 to 2016, such as “Gando (2016)^[32]” and “Kienast (2006),^[33]” marks the transition from basic pathology to clinical therapeutic strategies. The red cluster on the right consists predominantly of post-2020 publications, notably “Evans (2021)^[24]” and “Tang (2020),^[34]” representing the rapidly emerging research frontier following the COVID-19 pandemic. This cluster focuses on virus-induced coagulation dysregulation, thrombotic risk, and immune responses,

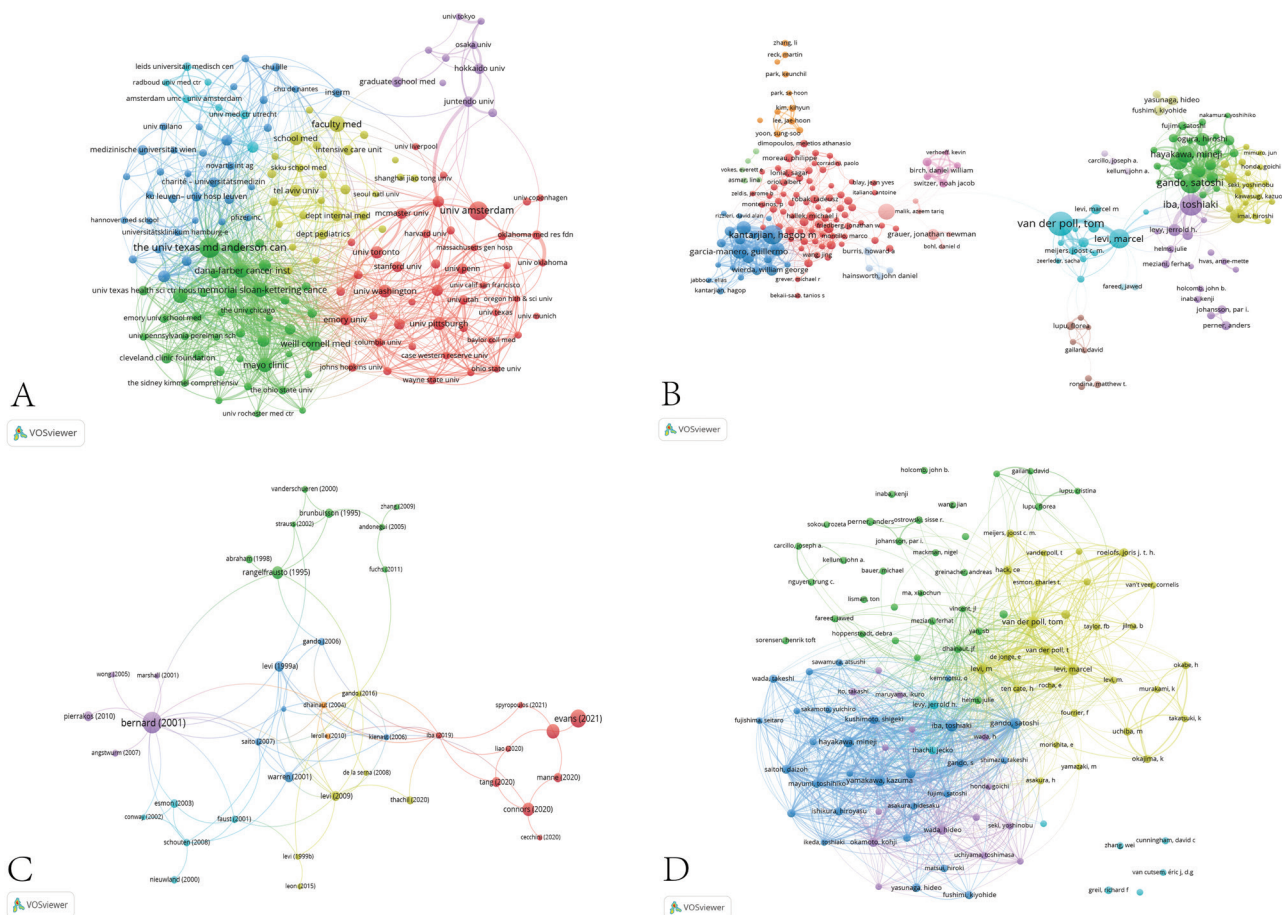


Figure 3. (A) Institutional collaboration network in sepsis-induced coagulopathy research. The network visualization reveals a globally decentralized yet locally integrated collaborative structure among major research institutions. Three distinct regional clusters emerge: North American (red), European (blue), and East Asian (green) consortia. Node size represents publication output, while the thickness of the connecting line indicates the intensity of collaboration. (B) Author collaboration network in sepsis-induced coagulopathy research. This co-authorship network map illustrates collaborative patterns among researchers, revealing the formation of knowledge communities and relational density across disciplinary groups. The network exhibits a multicentric structure, comprising several tightly connected research teams. (C) Co-citation network of highly cited publications in sepsis-induced coagulopathy research. This visualization maps the co-citation relationships among seminal publications, revealing the evolution of knowledge structures and intellectual pathways across different time periods. Node size corresponds to citation frequency, color indicates thematic clusters, and line thickness represents co-citation strength. (D) Co-citation network of highly cited authors in sepsis-induced coagulopathy research. This network visualization maps the intellectual structure of the field through co-citation relationships among influential authors. Node size represents citation frequency, colors distinguish between knowledge communities, and the thickness of the connecting lines indicates co-citation strength.

while maintaining substantial cross-links with traditional sepsis and DIC research, reflecting the pandemic's transformative impact on the field's intellectual structure. Overall, the network reveals a clear thematic evolution, progressing from early, basic mechanisms (1995–2005) to clinical management strategies (2005–2015) and ultimately to COVID-19-driven research fronts (2020 and beyond).

This co-citation network (Fig. 3D) visualization maps the collaborative relationships among highly cited authors in the research field. The yellow cluster, centered around Tom van der Poll, M. Levi, and Marcel Levi, represents the largest and most tightly connected group in the network, constituting the dominant force in theoretical and mechanistic research. These authors' sustained focus on fundamental pathological processes— inflammatory responses, coagulation imbalances, and immune activation—has resulted not only in substantial node size but also in exceptionally high connection density with other research groups, establishing this cluster as the structural anchor of the entire network. The thick connecting lines between this yellow cluster and the green cluster indicate strong co-citation relationships with

authors such as Vincent, Greinacher, and Yang, who focus on critical care, infection mechanisms, and clinical management. This pattern forms a dual-core structure within the network. The blue cluster consists primarily of Asian scholars, including Mineji Hayakawa, Kazuma Yamakawa, and Hideo Wada. Its tightly knit internal structure demonstrates the significant contributions of Japanese and East Asian researchers in acute coagulopathy management, diagnosis, and treatment guidelines. In contrast, the purple and light blue clusters represent independent developmental pathways in specific clinical subpopulations. The overall network exhibits a distinct “Euro-American center with Asian sub-center” pattern. Yet, the numerous and substantial intercluster connections indicate a high degree of international collaboration and efficient knowledge dissemination.

A journal-level analysis reveals the top 10 publications journals (Supplementary Table 4, <https://links.lww.com/ECCM/A116>). *Blood* emerged as the most influential journal (38,110 citations from 223 publications; impact factor = 21), followed by *Critical Care Medicine* (19,948 citations from 220 articles; impact factor = 7.7).

Keyword clustering and future research hotspots

This keyword co-occurrence network (Fig. 4A) reveals the internal structure of research topics, the formation mechanisms of hotspots, and the knowledge associations between different themes (The keyword list is provided in Supplementary Table 5, <https://links.lww.com/ECCM/A117>). The blue cluster on the left, “centered around sepsis,” “disseminated intravascular coagulation,” “inflammation,” and “fibrinolysis,” represents the most fundamental and extensively researched theme. The red cluster in the lower central region, featuring keywords such as “COVID-19,” “thrombocytopenia,” and “acute kidney injury,” clearly emerged following the global pandemic. The yellow cluster concentrates on “mortality,” “complications,” and “venous thromboembolism,” reflecting an expanded research focus toward clinical outcomes and complication management. The green cluster gathering around “chemotherapy” and “clinical trial” represents the specialized subfield of coagulation risk management.

This keyword evolution map (Fig. 4B) displays 3 distinct phase-based thematic zones. Keywords in cooler colors reflect the field’s early foundational focus, with terms such as “sepsis,” “inflammation,” “coagulopathy,” and “disseminated intravascular coagulation” forming the conceptual core that has maintained central importance throughout the research timeline. As the color spectrum transitions to intermediate tones, a group of keywords indicates the field’s expansion toward clinical application and risk assessment. These mid-phase terms—including “mortality,” “complications,” “venous thromboembolism,” and “pulmonary embolism”—represent a natural extension from basic mechanisms to clinical outcomes and risk management. The warm-colored zone contains numerous recent-phase keywords representing emerging hotspots typically driven by new disease patterns, clinical contexts, or global public health events. Terms such as “COVID-19,” “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),” “biomarker,” “prognosis,” and “intensive care” cluster in this warmer region, reflecting a rapid thematic expansion driven by emerging clinical needs that have led to structural transformation in the coagulation-infection intersection. These keywords have significantly enhanced cross-domain integration within the thematic network, resulting in more complex, multithematic interactions.

Discussion

Research trends and driving factors

With the evolution of the definition of sepsis (marked by 3 major revisions from Sepsis-1 in 1991 to Sepsis-3 in 2016), the conceptual understanding of SIC has also undergone a significant shift—from being viewed as a late-stage complication (DIC) to a distinct entity with early identifiable features (SIC). The pathophysiological basis of SIC lies in the complex interaction between the inflammation and coagulation cascades, characterized by the triad of vascular inflammation, platelet dysfunction, and endothelial injury.^[35] This dynamic interaction involves dysregulated cytokine release, NET-driven thrombin generation, and glyco-calyx shedding, collectively fostering a prothrombotic milieu that exacerbates microvascular dysfunction.^[36] The current SIC diagnostic criteria integrate indicators such as platelet count, prothrombin time-international normalized ratio (PT-INR), and Sequential Organ Failure Assessment, aiming to prevent irreversible organ damage by early identification of a hypercoagulable state.^[14] This paradigm shift in intervention aligns with the Sepsis-3 framework’s emphasis on timely, targeted therapy. Driven by the persistent global burden of sepsis and coagulation dysfunction as the core mechanism of multiorgan failure.

National research landscapes and academic leadership

Communication and cooperation between countries, institutions, and authors

The United States and Japan emerged as dominant contributors, yet their research priorities diverged markedly. The United States institutions focused on broad mechanistic themes while Japanese teams pioneered the standardization of diagnostics and pathophysiological investigations of DIC. Notably, China ranked second in productivity but lagged significantly in citations, highlighting the urgent need for China to prioritize research quality enhancement.

Tom van der Poll’s key works included “The immunopathology of sepsis and potential therapeutic targets”^[2] and “Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study.”^[37] As an international authority in sepsis research, van der Poll played a pivotal role in developing The Third International Consensus Definitions for Sepsis and

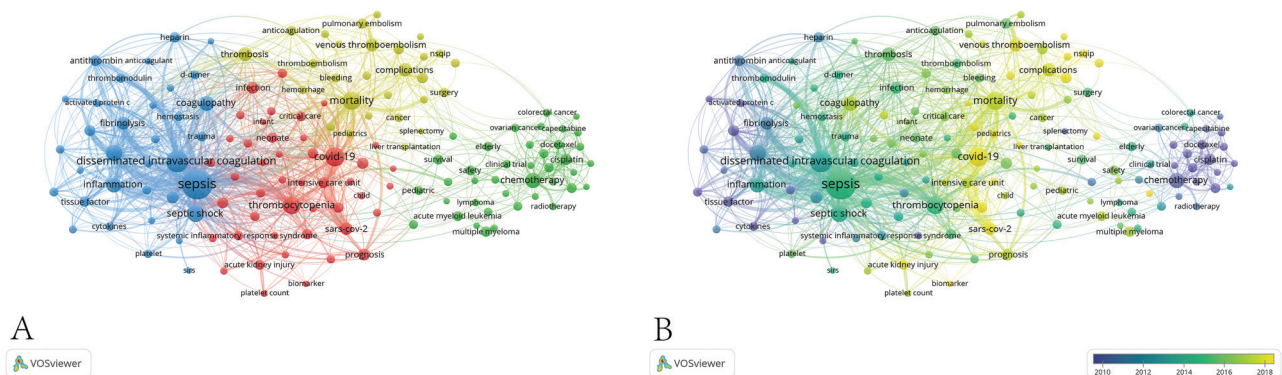


Figure 4. Visualization analysis of keywords. (A) Keyword co-occurrence network in sepsis-induced coagulopathy research. This network map reveals the thematic structure and knowledge associations within the research field. Node size corresponds to keyword frequency, connecting lines represent co-occurrence strength, and colors distinguish thematic clusters. (B) Temporal evolution of research themes in sepsis-induced coagulopathy. This keyword overlay visualization maps the chronological development of research hotspots using a color gradient, where cooler tones represent earlier-established themes and warmer tones indicate later-emerging frontiers.

Septic Shock (Sepsis-3) in 2016,^[38] which received 16,859 citations (Web of Science data). He has also made pioneering contributions to the field of sepsis immunology.^[39]

Toshiaki Iba, Satoshi Gando, and Hideo Wada are internationally recognized leaders in thrombosis and hemostasis, with profound influence on the mechanistic understanding, diagnosis, and therapeutic management of SIC. Among their landmark contributions, Iba et al. pioneered the conceptualization of SIC—a diagnostic framework aligned with the Sepsis-3 criteria (2016). They established a rapid and pragmatic clinical tool that effectively bridged mechanistic pathophysiology with bedside application.^[4] This innovation has fundamentally reshaped risk stratification and early intervention strategies in septic patients, addressing the critical need for timely recognition of coagulopathy in resource-limited settings. Their collective work had advanced understanding of coagulopathies through numerous influential publications.^[40–46]

Popular journals and development prospects

Publications on SIC are predominantly clustered in critical care, hematology, and coagulation-focused journals. As the flagship journal of the Society of Critical Care Medicine, *Critical Care Medicine* prioritizes high-impact translational research, including sepsis pathophysiology, organ dysfunction, and therapeutic innovation. Its emphasis on multidisciplinary approaches—integrating immunology, coagulation biology, and intensive care—has positioned it as a pivotal platform for disseminating SIC-related breakthroughs, such as the Japanese Association for Acute Medicine/ISTH diagnostic criteria and anticoagulant trials. Hematology and coagulation-specific journals offer in-depth mechanistic insights, but their scope remains confined to specialized fields. Moving forward, SIC research should prioritize broader engagement with clinical medicine, omics technologies, and multidisciplinary collaborations to foster cross-disciplinary innovation and accelerate translational progress.

Most popular articles on sepsis-induced coagulopathy

The most cited publication in SIC research is the landmark PROWESS trial by Bernard et al.,^[18] which evaluated the efficacy and safety of recombinant human activated protein C (rhAPC, drotrecogin alfa) in severe sepsis. This multicenter, double-blind, randomized controlled trial (RCT) demonstrated a 6.1% absolute reduction in 28-day mortality (24.7% vs. 30.8%, $P = 0.005$), establishing rhAPC as the first FDA-approved therapy targeting sepsis-associated coagulopathy. However, subsequent studies revealed increased bleeding risks and inconsistent efficacy in broader populations, leading to its withdrawal in 2011. Despite this, the PROWESS trial remains pivotal for catalyzing research into anticoagulant strategies and coagulation-inflammatory crosstalk in sepsis.

Meanwhile, the pathological mechanisms of hypercoagulability following COVID-19 infection, along with the assessment of thrombotic risk^[47] and clinical management strategies,^[48] have emerged as cutting-edge research foci in sepsis-associated coagulopathy in recent years.

Core research findings

Etiology and clinical management—catalytic impact of COVID-19

The marked increase in SIC publications during 2020 and 2021 coincided with the COVID-19 pandemic, during which coagulopathy emerged as a hallmark complication of severe SARS-CoV-2 infection, characterized by microvascular thrombosis and

elevated D-dimer levels.^[49] Early pandemic epicenters—Italy, the United States, and China—dominated COVID-19-associated SIC research during this period. This geographic concentration highlights how global health crises can temporarily redirect scientific priorities toward urgent clinical challenges, exemplified by the rapid investigation into heparin dosing optimization and endothelial injury biomarkers.

Autopsy studies revealed that thrombosis in critically ill patients may arise from immobilization-associated hypercoagulability and systemic inflammatory cascades, while concurrently confirming direct viral-induced endothelial injury as a pathogenic driver of microvascular dysfunction.^[50] To address the unmet clinical need for improving the poor COVID-19 outcomes, clinical researchers have spearheaded numerous trials evaluating anticoagulation regimens. Among these, the INSPIRATION trial—the first randomized controlled trial to systematically assess anticoagulant dosing in severe COVID-19 failed to establish an optimal therapeutic window for mitigating thrombotic events in critically ill cohorts.^[51] Nevertheless, its methodological rigor and negative findings catalyzed a paradigm shift, inspiring subsequent research across the continuum of care: from prehospital thromboprophylaxis protocols and in-hospital dose-escalation strategies to postdischarge extended anticoagulation regimens.^[52] These efforts collectively highlight the imperative for precision-guided, phase-specific interventions tailored to the dynamic thrombotic risk landscape of COVID-19 survivors.

Molecular mechanisms

The research landscape of SIC has progressed through distinct phases, evolving from early investigations of isolated coagulation abnormalities to contemporary paradigms that integrate immune and inflammatory pathways. The chronological development of key concepts exemplifies this evolution: initial focus on NETs and glycocalyx degradation established foundational mechanisms.^[53] At the same time, subsequent recognition of immunothrombosis and thrombo-inflammation revealed the complex interplay between coagulation and immunity in SIC pathogenesis.^[54]

NETs, composed of DNA, histones, and cytotoxic proteins, are released by activated neutrophils during sepsis and drive thrombosis through multiple synergistic mechanisms.^[55] NETs induce proinflammatory endothelial transformation and disrupt the glycocalyx barrier, thereby exposing tissue factor and initiating the extrinsic coagulation pathway. At the same time, their polyanionic surfaces directly activate factor XII (FXII) to trigger the intrinsic coagulation cascade and serve as scaffolds for coagulation factor assembly.^[56] Furthermore, NETs activate platelets via Toll-like-receptor 2/4 (TLR2/TLR4) mediated pathways, promote platelet-neutrophil aggregation, and disrupt anticoagulant balance by modulating the ADAMTS-13/vWF axis.^[57, 58] These interconnected mechanisms create a vicious cycle of inflammation-coagulation crosstalk, ultimately resulting in microvascular thrombosis and multiple organ dysfunction.

The glycocalyx, comprising proteoglycans, glycosaminoglycan chains, glycoproteins, and adherent plasma proteins, maintains vascular homeostasis by regulating vascular permeability, controlling microvascular tension, and preventing microvascular thrombosis.^[59] Glycocalyx degradation is a key determinant of endothelial dysfunction and is closely related to the pathophysiological cascade of sepsis. The shedding of the glycocalyx reduces circulating antithrombin levels, tilting the hemostatic balance toward a prothrombotic state characterized by uncontrolled thrombin generation and fibrin deposition.^[60] The hemodynamic stagnation exacerbated by microvascular thrombosis further

enhances platelet aggregation and immunothrombosis, leading to a vicious cycle of organ hypoperfusion and inflammation amplification.^[61] Emerging therapeutic strategies aim to counteract this cascade by targeting the regeneration of glycocalyx.^[62]

In recent years, the intricate interplay between inflammation and thrombosis has garnered significant scientific interest. This dual mechanism is classified as “immunothrombosis” in physiological contexts—a protective host defense that restricts pathogen dissemination via inflammation-induced coagulation—and as “thromboinflammation” in pathological states, where dysregulation leads to excessive clot formation and tissue damage.^[63] While immunothrombosis represents a vital synergy between coagulation and inflammatory pathways, its overactivation can trigger a self-perpetuating cycle of ischemia, amplified inflammation, and secondary tissue injury. This mechanistic insight helps explain the limited efficacy of conventional anticoagulant therapies, which fail to address the underlying immune dysregulation. Notably, beyond targeting platelets and the coagulation cascade, anti-inflammatory treatment has emerged as a promising therapeutic strategy.^[64] Since inflammation precedes the activation of the coagulation cascade and thrombin generation, modulating this upstream process may offer a safer anticoagulant approach by reducing the risk of bleeding complications.^[65] In this context, repurposing clinically approved anti-inflammatory drugs to treat dysregulated coagulation could represent an efficient strategy for preventing immunothrombosis-associated coagulopathies.^[66]

Biomarkers and prognostic

The biomarkers and prognostics cluster, dominated by keywords such as coagulopathy, prognosis, and SIC, highlights the research community's prioritization of early diagnosis and outcome prediction in sepsis-associated coagulation disorders. The conceptual shift from DIC to SIC underscores the clinical imperative to identify hypercoagulability before overt consumptive coagulopathy and multiorgan failure develop. While D-dimer remains a widely used biomarker for fibrinolytic shutdown, its limited sensitivity in early stages of SIC necessitates the exploration of novel markers. Emerging coagulation, inflammation, and endothelial markers such as thrombomodulin and vascular endothelial markers, soluble thrombomodulin, microvesicles, NETs, and angiotensin-2 have been extensively studied for diagnosing and managing DIC.^[67] The clinical adoption of these advancements remains constrained by the limitations of specialized laboratory expertise and advanced technologies. Furthermore, the intricate pathophysiological interplay between coagulation and inflammation undermines the diagnostic effect of individual biomarkers for SIC.^[68] Integrating machine learning with multimodal biomarker profiling redefines the prognostication of SIC. Algorithms enhance interpretability, which supports early, individualized interventions to improve outcomes for sepsis patients.^[69] Future advancements hinge on prospectively validating machine learning-augmented dynamic scores in multicenter trials and expanding biomarker panels to bridge the gap between mechanistic insights and actionable clinical interventions.

Pathophysiology and syndromes

The pathophysiology and syndromes cluster, dominated by sepsis and DIC, underscores the centrality of thrombotic-inflammatory crosstalk in SIC. The keyword DIC ranked second, reflecting its role as the terminal manifestation of uncontrolled coagulation, marked by microvascular thrombosis and consumptive coagulopathy. The prominence of ADAMTS-13—a protease that cleaves ultra-large vWF multimers to prevent

pathological platelet aggregation—highlights the cluster's focus on immune-thrombotic regulation. Severe ADAMTS-13 deficiency (thrombotic microangiopathies) drives vWF accumulation, exacerbating microcirculatory dysfunction by microthrombosis.^[70] Concurrently, antithrombin (formerly termed antithrombin III) remains pivotal, with mutations or acquired deficiencies amplifying thrombin generation and heparin resistance. These mechanisms are amplified by sepsis, which triggers a fibrinolytic shutdown via the overexpression of plasminogen activator inhibitor-1, thereby perpetuating organ hypoperfusion.^[71]

Limitations

This study has certain limitations. First, the inclusion of only English-language literature and the delayed indexing of preprints may introduce a selection bias. Second, the evolving conceptualization of SIC and the expanded scope of our literature search may have reduced the specificity of our bibliometric analysis by including publications that do not strictly align with the current definition of SIC. Nevertheless, our multidimensional approach provides a comprehensive SIC research evolution across 3 decades. By delineating research hotspots and frontiers, our findings empower researchers to prioritize translational pipelines from mechanistic discovery to therapeutic intervention while offering valuable insights for future investigations.

Conclusion

Over the past 30 years, research on SIC has achieved transformative advances, including epidemiology/clinical management, molecular mechanisms, biomarkers/prognostics, and pathophysiology. However, the translational chasm between mechanistic studies and clinical trials remains a formidable barrier, exacerbated by oversimplified animal models and heterogeneous patient populations. Besides, geographic inequities highlight systemic disparities in research capacity. These are compounded by disproportionate contributions from high-income regions versus limited outputs from high-burden, low-resource settings. Furthermore, transient surges in publication output during COVID-19 failed to catalyze sustained investment, underscoring the need for structured funding mechanisms to prioritize sepsis beyond pandemic urgency.

Future priorities could focus on precision intervention via artificial intelligence (AI)-augmented multiomics subphenotyping to optimize anticoagulant selection and timing, as well as mechanism-driven therapeutics targeting thromboinflammatory cascades to prevent organ injuries. By equitable global frameworks facilitate national collaboration to accelerate the translational loop from discovery to patient benefit. Collectively, these axes may bridge discovery-to-care translation, mitigating the global SIC burden.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Song B and Chen G contributed to conceptualization, methodology, formal analysis, investigation, data curation, writing the original draft, review and editing, visualization, and software. Kang H contributed to writing, review, and editing.

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Ethical approval of studies and informed consent

All studies included in this study followed the principles of the Declaration of Helsinki as revised in 2013.

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