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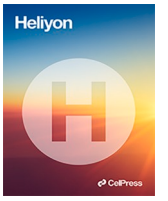

Review article

Global trends in research on endothelial cells and sepsis between 2002 and 2022: A systematic bibliometric analysis

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ABSTRACT

Sepsis is a systemic syndrome involving physiological, pathological, and biochemical abnormalities precipitated by infection and is a major global public health problem. Endothelial cells (ECs) dysfunction is a major contributor to sepsis-induced multiple organ failure. This bibliometric analysis aimed to identify and characterize the status, evolution of the field, and new research trends of ECs and sepsis over the past 20 years.

For this analysis, the Web of Science Core Collection database was searched to identify relevant publications on ECs in sepsis published between January 1, 2002, and December 31, 2022. Microsoft Excel 2021, VOSviewer software, CiteSpace software, and the online analysis platform of literature metrology (http://bibliometric.com) were used to visualize the trends of publications' countries/regions, institutions, authors, journals, and keywords.

In total, 4200 articles were identified and screened, primarily originating from 86 countries/regions and 3489 institutions. The USA was the leading contributor to this research field, providing 1501 articles (35.74 %). Harvard University's scientists were the most prolific, with 129 articles. Overall, 21,944 authors were identified, among whom Bae Jong Sup was the most prolific, contributing 129 publications. Additionally, Levi Marcel was the most frequently co-cited author, appearing 538 times. The journals that published the most articles were *SHOCK, CRITICAL CARE MEDICINE,* and *PLOS ONE*, accounting for 10.79 % of the total. The current emerging hotspots are concentrated on "endothelial glycocalyx," "NLRP3 inflammasome," "extracellular vesicle," "biomarkers," and "COVID-19," among others.

In conclusion, this study provides a comprehensive overview of the scientific productivity and emerging research trends in the field of ECs in sepsis. The evidence supporting the significant role of ECs in both physiological and pathological responses to sepsis is continuously growing. More in-depth studies of the molecular mechanisms underlying sepsis-induced endothelial dysfunction and EC-targeted therapies are warranted in the future.

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Abbreviations

EC	endothelial cell
SOFA	Sequential Organ Failure Assessment
WoSCC	Web of Science Core Collection
USA	United States of America
IF	impact factor
VE-cadherin	vascular endothelial cadherin
Rho	Ras homologous
Pyk2	proline-rich tyrosine kinase 2
Ang	angiopoietin
GTP	guanosine triphosphate
NO	nitric oxide
ADM	adrenomedullin
IL	Interleukin
CCl-2	chemokine ligand 2
CXCL-1	chemokine ligand 1
Fer-1	ferrostatin-1
Lip-1	liproxstatin-1
NLRP3	nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3
HMGB1	high mobility group protein B1
DIC	disseminated intravascular coagulation
PAI-1	plasminogen activator inhibitor 1
vWF	von Willebrand factor
ZO-1	zonula occluden-1
COVID-19	Coronavirus disease 2019
ACE2	angiotensin-converting enzyme 2
JAK	Janus kinase

1. Introduction

Sepsis is a complex syndrome usually caused by bacterial infection [1]. Over the years, defining sepsis has been difficult due to the disease's complexity in the clinical context and the biological and clinical heterogeneity of the septic population. Hence, the definition of sepsis has continuously evolved, reflecting a deeper understanding of its intricate pathophysiology. The consensus definition of sepsis transitioned from the systemic inflammatory response syndrome (SIRS) criteria with suspected infection (sepsis 1.0) to SIRS criteria combined with the presence of organ dysfunction (sepsis 2.0), and finally, to a dysregulated host response to infection leading to potentially life-threatening organ dysfunction (sepsis 3.0) [2–4]. The sepsis 3.0 definition underscores the integration of the Sequential Organ Failure Assessment (SOFA) score to characterize organ dysfunction. This highlights the central role of the non-homeostatic host response to infection, its increased lethality compared to that of mere infection, and the significance of early identification [4]. Globally, a total of 49 million individuals develop sepsis yearly, with nearly 11 million associated deaths [5]. Despite significant progress in comprehending the etiology and advancing new therapeutic strategies for sepsis, mortality rates have continued to be unacceptably high over the past few decades [6]. Moreover, various long-term dysfunctions, encompassing physical, psychological, and cognitive impairments, have increasingly emerged as the principal threats to the quality of life of sepsis survivors [7,8].

Sepsis impacts almost every organ and tissue, with endothelial cells (ECs) primarily encountering and responding to most of these insults. Upon stimulation, the expression of inflammatory cytokines, procoagulant factors, chemokines, tissue factors, and adhesion molecules is upregulated, thus promoting a shift in ECs toward a proinflammatory, procoagulant, pro-adhesive, and proapoptotic phenotype [9]. While these responses initially assist in combating inflammation, systemic and persistent activation of the endothelium may ultimately impair its normal structure and function. This includes the shedding of the glycocalyx, the loss of tight junctions, and extensive cell apoptosis and/or necrosis. The disrupted endothelial barrier function and activated coagulation system increase interstitial leakage, microvascular thrombosis, and tissue hypoxia, ultimately leading to life-threatening organ failure [10,11]. Hence, considerable attention has been focused on ECs by medical scientists worldwide to explore the mechanisms underlying endothelium damage and identify novel targets for the effective treatment of sepsis.

Recognition of the significant role of ECs in sepsis has resulted in many clinical trials and experimental studies, which have greatly improved our understanding of the complex pathophysiology of sepsis. However, there has been limited investigation into the specific patterns of these publications regarding their global research status and future research trends.

Bibliometrics is an important discipline that applies mathematical and statistical methods to obtain data on productivity rates, publication patterns, and characteristics. The research status and trends of a specific research domain can be visually described using co-authorship, co-occurrence, co-citation, and citation analyses. By mapping a knowledge domain, a bibliometric study can identify the distribution, internal collaboration, and productivity of researchers, countries/regions, affiliations, and journals and present

research hotspots and promising future directions. Therefore, this study aimed to systematically analyze research on endothelium and sepsis to identify hot topics and evolving trends in the field.

2. Materials and methods

2.1. Data sources and search strategies

The Web of Science Core Collection (WoSCC) database was initially searched on September 27, 2022, with an updated search performed on March 18, 2023. The search query was: TS= (endothelium* OR endothelial cell* OR ECs OR endothelia) AND TS= (sepsis OR septic shock OR endotoxemia OR severe sepsis OR SIRS OR systemic inflammatory response syndrome). The time frame for retrieval spanned from January 1, 2002, to December 31, 2022. The document type was restricted to "articles," and the search was confined to publications in English. Comprehensive data from the included publications, encompassing the year of publication, author, title, source, number of citations, abstract, address, affiliation, document type, keywords, and cited reference count, were systematically gathered from the WoSCC.

2.2. Data analysis

Bibliographic data were imported into Microsoft Excel 2021, VOSviewer software, CiteSpace software, and an online analysis platform for literature metrology (http://bibliometric.com). Microsoft Excel 2021 was used to analyze the trends in the number of publications in different countries or regions. The VOSviewer software (Leiden University, Leiden, The Netherlands, version 1.6.18) was utilized to construct and visualize bibliometric networks. These networks were generated based on a co-authorship analysis of countries and institutions, with the node size in the maps indicating the extent of collaboration. Co-citation was analyzed as the simultaneous citation of two items, such as authors, documents, or journals, in a third article. A visual analysis based on the co-citation of authors was conducted. The frequency of references to the same article is reflected in the positive correlation of the links between nodes. Furthermore, the CiteSpace software facilitated the creation of maps showcasing the co-occurrence of keywords. All keywords were categorized into different clusters to delve into the knowledge structure within this field. Burst keywords were identified using the CiteSpace software, with the primary parameters being time slicing (2002–2022), years per slice (1), and top N per slice (50).

3. Results

3.1. Global trend of publication outputs and citation number

A total of 4200 articles related to ECs and sepsis were extracted, and Fig. 1 detailed our search and selection process. As illustrated in Fig. 2, the number of global publications has steadily increased, with annual publications increasing from 156 in 2002 to 250 in 2022. These articles were cited 149,210 times by March 18, 2023, and the annual number of citations rose from 89 in 2002 to 14,695 in

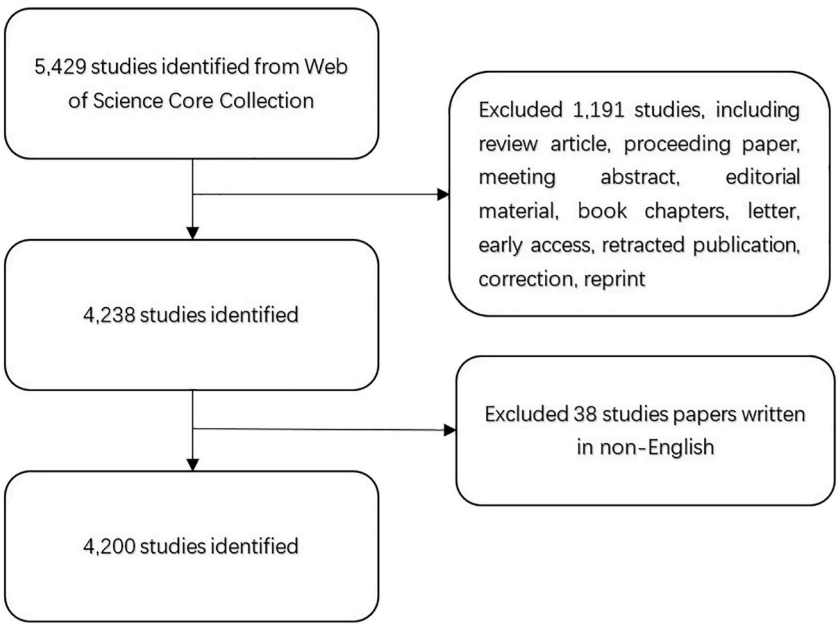

Fig. 1. Flow chart of the literature search, filtering, and selection of included publications.

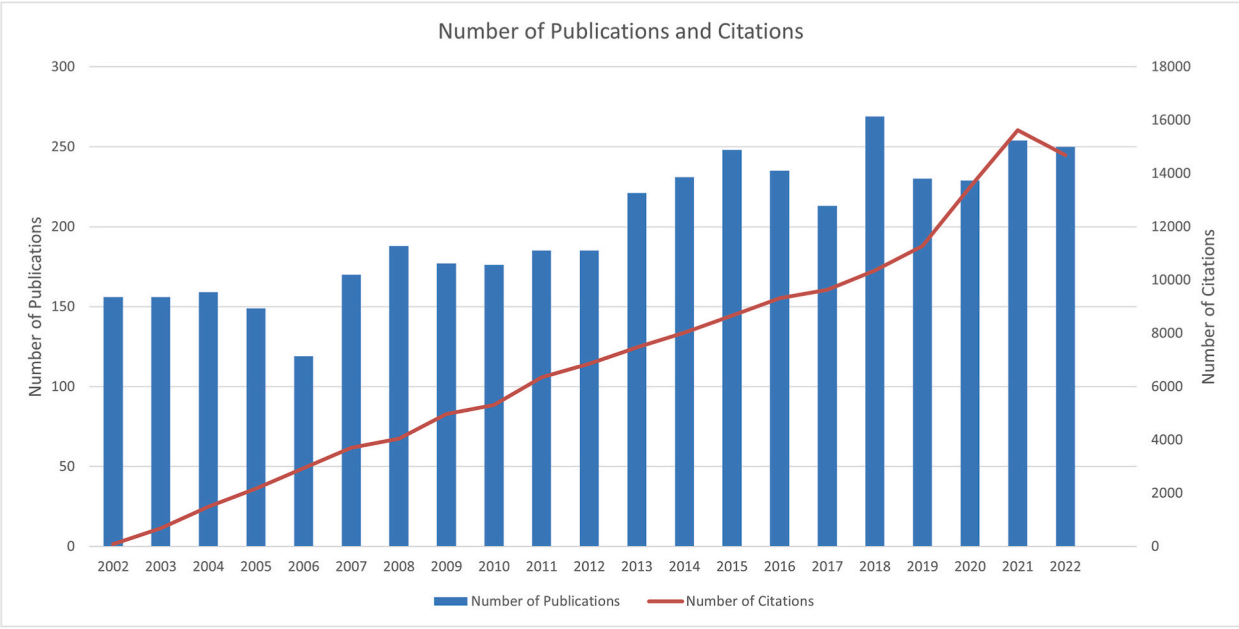

Fig. 2. Publications and citation numbers of articles related to endothelial cells in sepsis by year over the past 20 years.

2022.

3.2. Analysis of the contribution of countries/regions to the global literature

Eighty-six countries/regions participated in the 4200 publications, with the USA ranking first (1501/35.74 %), followed by China (766/18.24 %), Germany (488/11.62 %), Japan (295/7.02 %), and Canada (245/5.83 %) (Fig. 3A). The number of publications in China increased rapidly (Fig. 3B), with nearly 18 times more articles published in 2022 than in 2002. Since 2018, China has surpassed the USA and ranked first in the number of annual publications. Fig. 3C and D shows a map of co-authorship between the major countries in this research field, with the USA playing a central role in bridging cooperation among countries.

3.3. Analysis of institutions

As shown in Table 1, Harvard University was the most prolific among the 3489 institutions from which the publications originated (n = 129). Kyungpook National University ranked second, with 125 publications, while the French Institute of Health and Medical Research (INSERM) (n = 119) ranked closely behind. Among the top ten most productive institutions, five were located in the USA, and two were in France and the Netherlands.

As illustrated in Fig. 4A, the co-authorship visualization of institutions with a minimum of ten articles was performed, and 202 institutions met this criterion. A close cooperation exists between Harvard University and the Beth Israel Deaconess Medical Center, and between the University of Amsterdam and the University of Oxford. Kyungpook National University and Daegu Haany University in South Korea actively cooperated.

3.4. Analysis of authors

In total, 21,944 authors coauthored 4200 publications, and the average number of authors per paper was 5.22. As shown in Table 2, the authors with the highest number of publications were Bae Jong Sup (n = 129/3.07 %), Ku Sae Kwang (n = 66/1.57 %), Lee Wonhwa (n = 52/1.24 %), Van Der Poll Tom (n = 48/1.14 %), and Levi Marcel (n = 32/0.76 %). The H-index is an author-level metric that measures the productivity and citation impact of a scientist's or scholar's publications [12]. Among the top ten most productive authors, Levi Marcel, Esmon Charles T, Van Der Poll Tom, and Malik Asrar B had the highest H-index values (130, 115, 106, and 105, respectively).

The outcomes of the co-citation analysis are depicted in Fig. 4B. The size of each node on the map is directly proportional to the frequency with which the authors have been cited. Among the 71,199 authors, 222 were cited more than 50 times. The most frequently cited authors were Levi Marcel (538 times), followed by Bae Jong Sup (509 times) and Aird WC (502 times).

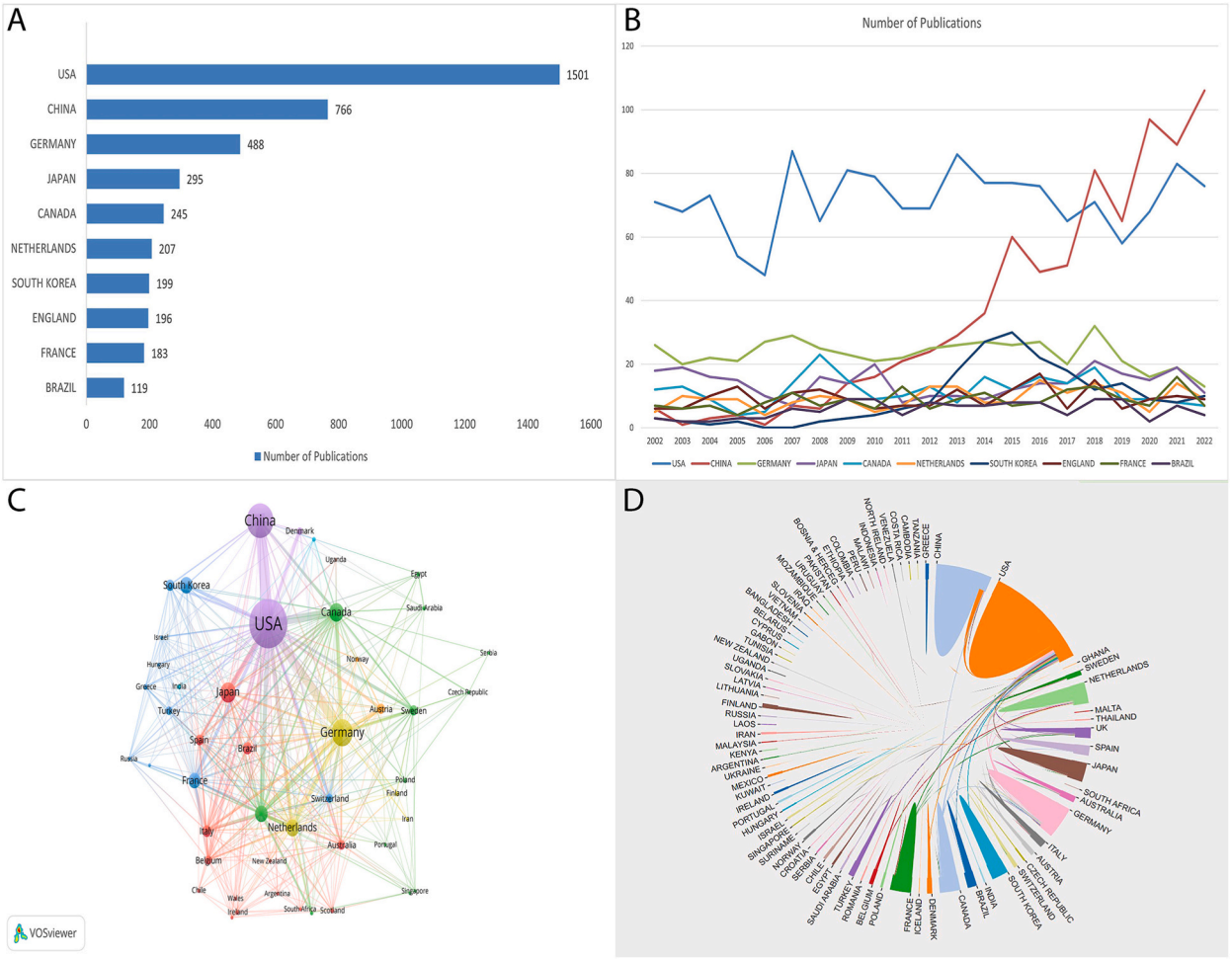

Fig. 3. Contributions of the most productive countries/regions to endothelial cells and sepsis research. (A) Number of publications of the top 10 countries; **(B)** annual publication number growth of the top 10 countries; **(C)** international collaboration of the most productive countries/regions; **(D)** The cooperation of countries/regions in research scope on endothelial cells and sepsis from 2002 to 2022.

Table 1
The top ten most productive institutions.

Rank	Institution	Country	Total Citations
1	HARVARD UNIVERSITY	USA	129
2	KYUNGPOOK NATIONAL UNIVERSITY	South Korea	125
3	INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE INSERM	France	119
4	UNIVERSITY OF AMSTERDAM	Netherlands	111
4	UDICE FRENCH RESEARCH UNIVERSITIES	France	111
6	UNIVERSITY OF CALIFORNIA SYSTEM	USA	107
7	HARVARD MEDICAL SCHOOL	USA	98
8	ACADEMIC MEDICAL CENTER AMSTERDAM	Netherlands	95
9	UNIVERSITY OF TEXAS SYSTEM	USA	94
10	PENNSYLVANIA COMMONWEALTH SYSTEM OF HIGHER EDUCATION PCSHE	USA	90

3.5. Analysis of journals

The 4200 retrieved articles were published in 948 academic journals. The journal *SHOCK* (178/4.24 %, impact factor [IF]: 3.1, 2022) had the highest number of publications in this field, followed by *CRITICAL CARE MEDICINE* (143/3.40 %, IF: 8.8, 2022), and *PLOS ONE* (132/3.14 %, IF: 3.7, 2022).

Bradford's law states that if scientific journals are arranged according to publication output and divided into three groups on a given subject, they may be divided into a nucleus of periodicals and two zones containing the same number of articles. The number of

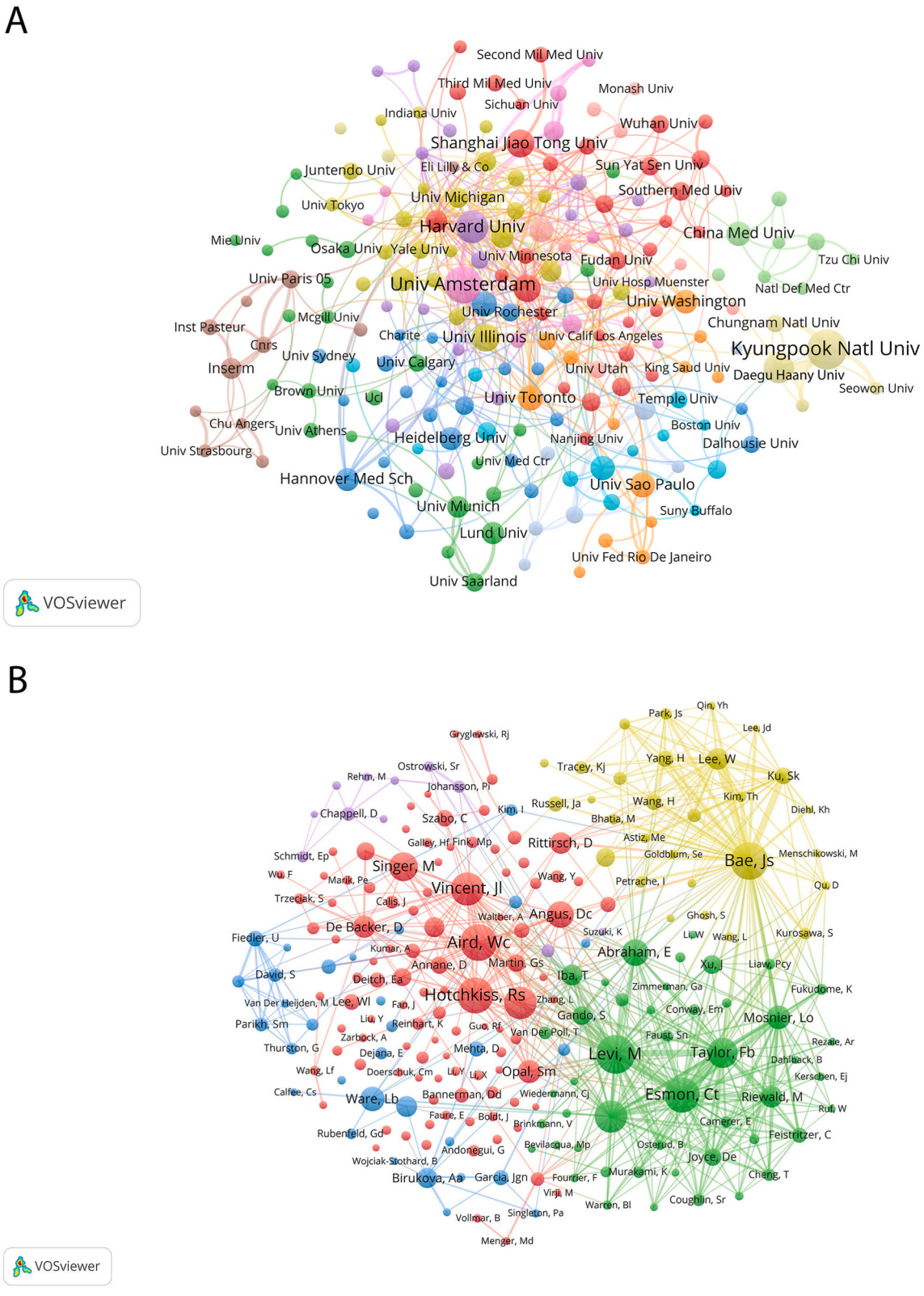

Fig. 4. **(A)** Co-authorship analysis of the institutions with a minimum of ten articles in the field of endothelial cells and sepsis; **(B)** Co-citation visualization map of authors with more than 50 times.

Table 2
The top ten most prolific authors.

Rank	Author	Country	Institution	Number of Publications	H-index
1	Bae, Jong-Sup	South Korea	Kyungpook National University	129	47
2	Ku, Sae Kwang	South Korea	Daegu Haany University	66	47
3	Lee, Wonhwa	South Korea	Sungkyunkwan University	52	32
4	Van Der Poll, Tom	Netherlands	University of Amsterdam	48	106
5	Levi, Marcel	Netherlands	Academic Medical Center, Amsterdam	32	130
6	Lehmann, Christian	Canada	Dalhousie University	26	26
7	Malik, Asrar B.	USA	University of Illinois System	25	105
8	Esmon, Charles	USA	Oklahoma Medical Research Foundation	24	115
9	Aird, William C.	USA	Beth Israel Deaconess Medical Center	22	59
10	Griffin, John H.	USA	Scripps Research Institute	22	90

periodicals in the nucleus and subsequent zones will be in the proportion of $1:n:n^2$ [13]. The top 23 journals published 1378 papers between 2002 and 2022, approximately one-third of the total number of publications. Based on Bradford's law, these 23 journals were defined as the "core journals" in this field (Table 3). Among these journals, except for the *JOURNAL OF SURGICAL RESEARCH* (53/1.26 %, IF: 2.2, 2022), all others had an IF greater than three, and *INTENSIVE CARE MEDICINE* had the highest IF (38.9, 2022). These journals mainly cover critical care medicine, hematology, immunology, peripheral vascular disease, and cellular biology.

The dual-map overlay of journals delineates the research position relative to the principal research disciplines, citing journals on the left and cited journals on the right. Furthermore, the color-coded paths between them demonstrate the cited relationships [14]. Fig. 5 illustrates four primary reference pathways. The orange and green paths indicate that articles published in "Molecular, Biology, Genetics" and "Health, Nursing, Medicine" journals are frequently cited by journals within the same disciplines. Additionally, the ellipse symbolizes the number of journal publications, with *CRITICAL CARE MEDICINE* and *JOURNAL OF BIOLOGICAL CHEMISTRY* leading in the "Health, Nursing, Medicine" and "Molecular, Biology, Genetics" categories among the cited journals, respectively.

3.6. Analysis of keywords

A total of 12,301 keywords in this field were identified using the VOSviewer software. The most frequently encountered keywords in the retrieved documents included "sepsis," "endothelial cells," "inflammation," "expression," "activation," "lipopolysaccharide," "cells," "acute lung injury," "dysfunction," and "apoptosis" (Table 4). Outcomes from the keyword cluster analysis are depicted in Fig. 6A. The analysis identified the following eight clusters: septic shock (Cluster #0), nitric oxide (Cluster #1), endothelial cells (Cluster #2), acute lung injury (Cluster #3), activated protein C (Cluster #4), endothelial glycocalyx (Cluster #5), adhesion molecules (Cluster #6), and thrombin thrombomodulin complex (Cluster #7).

Timeline viewer is based on the evolutionary trajectory of keywords in a certain field, which can show the stage characteristics and development of keywords in each cluster. Fig. 6B is the timeline viewer of ECs and sepsis based on CiteSpace software, which visually illustrates the phased hotspots and evolution track of the research from the time dimension. Each node represents a keyword, and the

Table 3
The top 23 journals with the most publications.

Rank	Journal Title	Country	Records	IF (2022)
1	SHOCK	USA	178	3.1
2	CRITICAL CARE MEDICINE	USA	143	8.8
3	PLOS ONE	USA	132	3.7
4	CRITICAL CARE	USA	104	15.1
5	BLOOD	USA	69	20.3
6	AMERICAN JOURNAL OF PHYSIOLOGY LUNG CELLULAR AND MOLECULAR PHYSIOLOGY	USA	64	4.9
7	THROMBOSIS AND HAEMOSTASIS	Germany	62	6.7
8	JOURNAL OF IMMUNOLOGY	USA	60	4.4
9	JOURNAL OF SURGICAL RESEARCH	USA	53	2.2
10	SCIENTIFIC REPORTS	England	51	4.6
11	FRONTIERS IN IMMUNOLOGY	Switzerland	46	7.3
11	INFLAMMATION	USA	46	5.1
13	JOURNAL OF BIOLOGICAL CHEMISTRY	USA	38	4.8
13	JOURNAL OF THROMBOSIS AND HAEMOSTASIS	England	38	10.4
15	INTENSIVE CARE MEDICINE	Germany	37	38.9
16	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS	USA	36	3.1
16	THROMBOSIS RESEARCH	England	36	7.5
18	JOURNAL OF LEUKOCYTE BIOLOGY	USA	34	5.5
19	MICROVASCULAR RESEARCH	USA	32	3.1
20	INTERNATIONAL IMMUNOPHARMACOLOGY	Netherlands	31	5.5
21	AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE	USA	30	24.7
22	CYTOKINE	England	29	3.8
22	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	USA	29	11.1

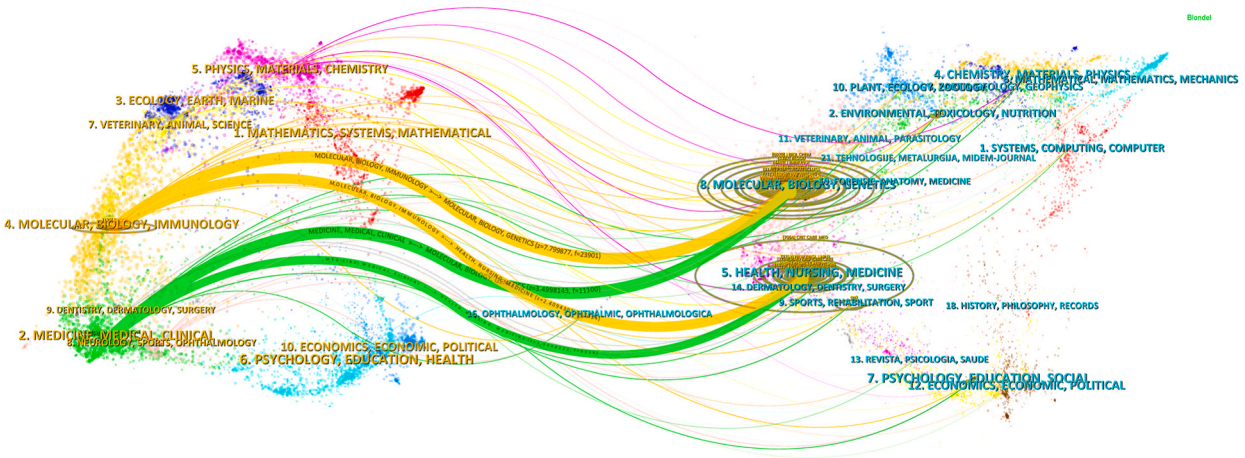

Fig. 5. The dual-map overlay of journals on endothelial cells and sepsis. The left part is citing journals and the right part is cited journals. Colored curves reveal paths of references originating from the citing component maps and pointing to the cited component maps. The thickness of the curves between them is proportional to the z-score-scaled frequency of citation. The citing and cited articles are divided into numerous thematic areas. Each area is determined by a cluster of journals belonging to the area, and is labeled by the most common terms from the titles of the underlying journals. The size of the yellow ellipse in the figure is positively correlated with the number of publications corresponding to a journal. The longer the horizontal axis of the ellipse, the more authors it represents; the longer the vertical axis of the ellipse, the more papers the journal publishes. (Among the cited journals in the fields of 'Health, Nursing, Medicine', *CRITICAL CARE MEDICINE*, *NEW ENGLAND JOURNAL OF MEDICINE*, and *AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE* were the most cited journals. And among the cited journals in the fields of 'Molecular, Biology, Genetics', *JOURNAL OF BIOLOGICAL CHEMISTRY* ranked first, followed by *BLOOD* and *JOURNAL OF IMMUNOLOGY*).

Table 4
The top 20 keywords.

Rank	Keyword	Count
1	sepsis	2546
2	endothelial cells	1271
3	inflammation	957
4	expression	775
5	activation	634
6	lipopolysaccharide	425
7	cells	369
8	acute lung injury	368
9	dysfunction	355
10	apoptosis	297
11	injury	288
12	NF kappa B	264
13	tumor-necrosis-factor	257
14	nitric-oxide synthase	256
15	in vivo	250
16	oxidative stress	246
17	endotoxin	242
18	coagulation	234
19	mechanisms	231
20	permeability	230

annual ring of the node indicates the appearance time of the keyword. From 2002 to 2022, certain research areas within the eight clusters have seen a decrease in focus, with the principal keywords being " superoxide," "adhesion molecular 1," "cholesterol," "crystal structures," and "platelet-activating factor." Conversely, several emerging research fields have been identified, marked by key terms such as " biomarkers," "extracellular vesicles," "syndecan-1," "NLRP3 inflammasome," and "microRNAs." Burst keywords signify leading-edge topics and potential hotspots in a given field. Fig. 6C illustrates that, during this period, the burst keywords predominantly included "extracellular vesicles," "NLRP3 inflammasome," "microRNAs," "endothelial glycocalyx," and "angiopoietin 2."

4. Discussion

ECs are widely recognized as pivotal components in the pathophysiology of sepsis, and focusing on ECs offers significant promise

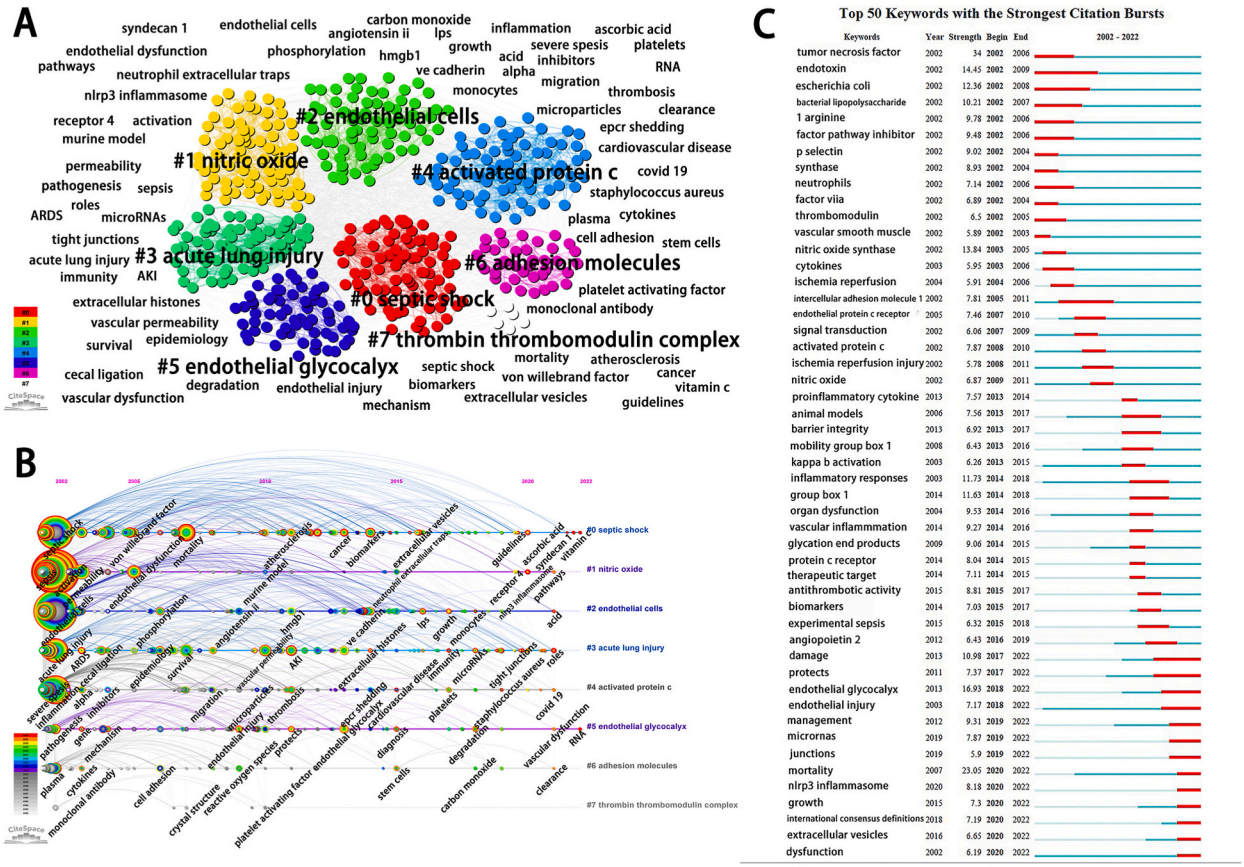

Fig. 6. The network mapping of keywords used in publications on endothelial cells in sepsis. (A) Keyword co-occurrence map; **(B)** CiteSpace visualization map of timeline viewer; **(C)** The top 50 keywords with the strongest citation bursts. The blue squares represent the years in which keywords had citation; the red squares stand for the years in which keywords had citation bursts.

for creating therapies for sepsis. Numerous experimental and clinical studies have been performed to illustrate the pivotal role of ECs in sepsis, with 4200 articles published in the last 20 years. The USA ranked first regarding the number of publications. Five institutions (Harvard University, University of California System, Harvard Medical School, University of Texas System, and Pennsylvania Commonwealth System of Higher Education) and four researchers (Esmon Charles T, Malik Asrar B, Griffin John H, and Aird William C) topped the ranking lists. The dominance of the USA in this field is evident. Furthermore, China has demonstrated exponential growth in publications, thereby becoming a crucial force in advancing this research. The robust increase in Chinese publication output can be attributed to the heightened focus of scientists in this area and the escalation in funding support.

Research on the role of ECs in sepsis has increasingly adopted a collaborative approach. The United States has been involved in the highest number of international collaborations. This trend may be attributed to that the significant presence of renowned institutions and researchers in this field within the United States, facilitating numerous scientific breakthroughs in EC and sepsis research to be first identified there. *SHOCK*, *CRITICAL CARE MEDICINE*, and *PLOS ONE* were the three most productive journals in EC and sepsis research. All 23 core journals were based in English-speaking or developed countries, and 15 of these journals were headquartered in the USA. This aligns with the findings of previous studies, underscoring the notion that researchers from English-speaking countries possess a distinct advantage, as their research findings are more frequently published in English-language scientific journals [15]. Furthermore, it can be hypothesized that publication output might be correlated with national research funding. Countries investing more in scientific research tend to have higher publication outputs compared to those with fewer investments [15,16].

4.1. Permeability of ECs

A semi-permeable barrier formed by ECs is crucial for controlling the permeability and distribution of water, cells, and molecules from circulation into tissues and maintaining vascular homeostasis and normal organ function [17]. ECs are excessively activated by inflammatory factors and endotoxins, leading to a ubiquitous loss of endothelial barrier integrity during sepsis. This results in a global increase in endothelial permeability syndrome, characterized by edema formation and systemic hypotension that endangers organ perfusion [18]. Endothelial permeability is primarily maintained by the glycocalyx, extracellular matrix, and intercellular junctions, including gaps, adherens, and tight junctions [19]. The endothelial glycocalyx, a mesh-like layer composed of proteoglycans and

glycoproteins, shields ECs from the spontaneous adhesion of leukocytes and platelets in a physiological state. Laminin polymers interact with collagen IV polymers secreted by ECs to form the basement membrane [20].

The extracellular matrix contributes to signaling pathways that favor cell adhesion, thereby regulating endothelial integrity and vascular barrier function. Neighboring EC cytoplasms are directly connected through gap junctions. Endothelial adherens junctions, formed by vascular endothelial cadherin (VE-cadherin), are crucial in controlling endothelial barrier function. During sepsis, inflammatory cytokines enhance Ras homologous (Rho) activity and activate the tyrosine kinases Src and proline-rich tyrosine kinase 2 (Pyk2). This activation results in the phosphorylation and endocytosis of VE-cadherin, thereby promoting an increase in vascular permeability [21,22]. The endothelial tight junction, comprising occludins, claudins, and junctional adhesion molecules, experiences disruption in sepsis, as indicated by the downregulation of tight junction protein levels [23]. Furthermore, during sepsis, under the activation and guidance of ECs, leukocytes traverse the vascular endothelium to engage with inflammatory foci [24]. For decades, vascular leakage has been thought to be a natural consequence of leukocyte extravasation in the defense against inflammation [25]. However, recent research indicates that vascular leakage and leukocyte emigration occur independently in blood vessels [26,27]. The fact that leukocyte traffic and vascular permeability can be regulated separately may establish the modulation of vascular leakage and tissue edema without compromising the immune response as a viable therapeutic target in sepsis [28]. In addition, the angiopoietin (Ang)- tyrosine kinase Tie2 signaling axis is crucial for the maintenance of endothelial integrity under physiological conditions. Ang-1 promotes EC survival and inhibits vascular leakage by suppressing the expression of the transcription factor Foxo1 and enhancing the phosphorylation of Tie2 [29,30]. Activation of Tie2 stimulates the Rho family GTPases, leading to the reinforcement of the cytoskeleton, which in turn enhances the barrier function of the endothelium [31]. Conversely, overexpression of Ang-2 by inflammatory cytokines leads to deleterious vascular effects and induces sepsis-like hemodynamic alterations in mice [32]. Therefore, targeting the Ang-Tie2 signaling axis may offer a promising treatment strategy. Nitric oxide (NO) has been linked to increased vascular permeability, and the pharmacological inhibition of NO production shows beneficial hemodynamic effects in animal models of sepsis [33–35]. Adrenomedullin (ADM) significantly influences inflammation, vascular tone, and endothelial barrier function [36]. Adrecizumab, an anti-ADM antibody, protects the endothelial barrier function by antagonizing the N-terminal of ADM, indicating a novel and promising approach to sepsis treatment [37,38]. Novel approaches to modulate the functionality and integrity of the primary molecular determinants of endothelial permeability during sepsis are expected to be translated into larger randomized controlled clinical trials in the near future.

4.2. Endothelial glycocalyx

The glycocalyx, covering the apical membrane of ECs, is a ubiquitous structure consisting of sulfated proteoglycans, hyaluronan, glycoproteins, and plasma proteins [39]. The endothelial glycocalyx is a critical mediator of vascular permeability, inflammation, coagulation, and circulatory tonicity [40]. In severe sepsis, the glycocalyx undergoes degradation due to the activation of various enzymes or reactive oxygen species [41]. This endothelial glycocalyx degradation consequently leads to capillary leakage, edema, progressive inflammation, platelet aggregation, coagulopathy, loss of vascular tone and responsiveness, and ultimately, end-organ damage and potential death [42]. As depicted in Fig. 6B, the research of endothelial glycocalyx mainly focuses on its functional analysis and related mechanisms. The main keywords include "pathogenesis," "gene," "mechanism," "endothelial injury," "protects," "diagnosis," "degradation," "vascular dysfunction," and "RNA."

Glycocalyx degradation products are promising indicators of endothelial damage during sepsis. Several studies suggested that modulation of glycocalyx integrity provided therapeutic benefits in sepsis [43]. Heparin protects against glycocalyx degradation via mobilizing syndecan-1 to reconstitute the protective network of proteoglycans and reconstruct the vascular endothelial barrier, thereby restoring endothelial function [44,45]. Furthermore, it protects the glycocalyx from shedding by suppressing heparinase activity and inflammation, attenuating sepsis-associated acute lung injury, and improving survival [46]. Nevertheless, in clinical practice, anticoagulant therapies for sepsis have not been systematically studied due to the increased risk of hemorrhage. Moreover, glucocorticoids, tranexamic acid, ulinastatin, and matrix metalloproteinase inhibitors benefit endothelial glycocalyx stability [47–49]. Several recent clinical trials have suggested that restricted fluid resuscitation strategies and plasma resuscitation during sepsis may be beneficial to protecting endothelial glycocalyx integrity [50–52]. Additionally, sphingosine 1-phosphate is associated with positive outcomes in septic shock due to its protective effects on the glycocalyx [53,54].

4.3. Endothelial inflammation in sepsis

ECs are both the source and target of inflammation during sepsis [55]. During sepsis, pattern recognition receptors and downstream inflammatory pathways are activated, resulting in an inflammatory response in ECs [10]. ECs are driven toward a proinflammatory phenotype characterized by the secretion of a large amount of interleukin (IL)-6, IL-8, chemokine ligand −2 (CCl-2), and chemokine ligand −1 (CXCL-1). IL-6 increases endothelial permeability by inducing the loss of junctional localization of VE-cadherin and zonula occluden-1 (ZO-1) [56]. Vaspin, N-arachidonoyl dopamine, and bone morphogenetic protein-binding endothelial regulators have exhibited anti-endothelial inflammatory properties in experimental animal models of sepsis [57–59]. Additionally, autophagy and ferroptosis have regulated the endothelial inflammatory response by downregulating proinflammatory cytokines and modulating immunogenicity [60,61]. Autophagy inducers, such as minocycline and rapamycin, and ferroptosis inhibitors, including ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1), have been effective in reducing inflammatory cytokine release and organ injury in experimental sepsis models [62–64]. Numerous studies have elucidated the important role of inflammasomes in sepsis, with the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 (NLRP3) inflammasome being the most extensively

investigated member of this class of receptors [65]. Activation of the NLRP3 inflammasome triggers the production and secretion of potent proinflammatory cytokines such as IL-1β, IL-18, and high mobility group protein B1 (HMGB1). These cytokines promote leukocyte adhesion and changes in endothelial permeability, thereby, inducing an inflammatory response [66,67]. Several studies have observed that inhibiting the activation of the NLRP3 inflammasome attenuates multi-organ injury in septic animals, underscoring the significance of the NLRP3 inflammasome as a promising target for endothelial dysfunction in sepsis [68,69].

Endothelial cell-derived extracellular vesicles (EVs) have regulated inflammatory responses [70], endothelial barrier function, and the coagulation cascade in sepsis. The secretion of EVs increases in response to endotoxin or inflammatory cytokine stimulation [71, 72]. EVs demonstrate a bidirectional regulatory effect on inflammation; they aggravate endothelial inflammatory responses by activating neutrophil adhesion to the endothelium and stimulating neutrophil extracellular traps [71]. They reportedly exert anti-inflammatory effects by attenuating NF-κB activation and nuclear translocation [73]. Elevated plasma exosome levels are associated with increased mortality and sepsis progression [74,75]. Additionally, it has been observed that the contents of EVs change depending on the disease condition [76]. Therefore, EVs are promising candidates for novel biomarkers in sepsis. Furthermore, due to their unique ability to carry small molecules to distant cells and modify the function of targeted cells, EVs are potential therapeutic targets [76]. Although significant progress has been made in understanding EVs' role in sepsis, substantial knowledge gaps remain regarding the secretion kinetics of EVs during different sepsis stages and the role of various EV components in sepsis [77].

4.4. ECs and the coagulation cascade in sepsis

Under physiological conditions, ECs provide different cell membrane-associated components to balance anticoagulant and fibrinolytic functions [78]. In sepsis, damage to the endothelial glycocalyx, reduction of endothelial thrombomodulin, and downregulation of plasma anticoagulant proteins activate the coagulation cascade and compromise anticoagulation potential [79]. Activation of coagulation is an essential component of the host's defense against pathogens; nevertheless, exaggerated activation may contribute to microvascular thrombosis and organ dysfunction and eventually develop into disseminated intravascular coagulation (DIC) [80,81].

During sepsis, the endothelium regulates the clotting cascade through the expression of thrombomodulin, activated protein C, tissue factor, plasminogen activator inhibitor 1 (PAI-1), microparticles, antithrombin, von Willebrand factor (vWF), and interactions with platelets [82–84]. ECs primarily synthesize thrombomodulin and are intricately linked with thrombin-mediated activation of protein C [85]. Activated protein C is a crucial inhibitor, limiting coagulation and managing thrombosis by proteolytically inactivating cofactors Va and VIIIa in sepsis [86]. PAI-1 is pivotal in suppressing fibrinolysis, as it binds to tissue plasminogen activator, thereby urokinase plasminogen activator and facilitating the development of disseminated intravascular coagulation (DIC) in patients with sepsis [87,88]. Elevated levels of PAI-1 in ECs are associated with hindered fibrinolysis and may lead to widespread microvascular thrombus formation during septic shock [9]. Furthermore, recent studies have underscored that inflammasome activation provokes endothelial inflammation and stimulates the release of coagulation factor III, the primary initiator of coagulopathy in sepsis, thus initiating the blood coagulation cascade [89].

Recent clinical trials have demonstrated that the modulation of coagulation is clinically valuable in the treatment of sepsis and the prevention of sepsis-induced DIC. Moreover, low-dose heparin, tissue factor pathway inhibitors, antithrombin III, and thrombomodulin have shown promising potential to regulate the endothelial coagulation pathway in animal studies; however, more clinical trials are needed to assess their therapeutic role in patients with sepsis [90–92].

4.5. Endothelial biomarkers in sepsis

During sepsis, elevated levels of endothelial molecules are detected in the blood due to functional and structural changes in ECs, which may be used to diagnose infection, prognostication, and therapeutic guidance. Syndecan-1, ADM, Ang-1/-2, thrombomodulin, heparanase-1/-2, vWF, endocan, soluble VE-cadherin, occludin, and zonula occluden-1 (ZO-1) are associated with both sepsis presence and severity [53,93–95] Syndecan-1, a transmembrane heparan sulfate proteoglycan in glycocalyx, was elevated in plasma due to sepsis-induced endothelial damage [96], reflecting glycocalyx damage and hence a superficial endothelial disruption. In addition, syndecan-1 levels may be conducive to predicting organ failure, DIC, coagulation disorders, and fluid requirements in patients with sepsis [97]. Thrombomodulin has been used to monitor DIC and multiple organ dysfunction syndromes in patients with sepsis [95]. Several studies have reported that the plasma concentrations of monocyte chemoattractant protein 1, soluble urokinase plasminogen activator receptor, and pentraxin-3 have prognostic and diagnostic value [98,99]. Additionally, non-coding RNAs, including miRNAs and long non-coding RNAs, are new types of endothelial biomarkers with recent advances in biotechnology [100,101]. Non-coding RNAs regulate various pathways involved in gene expression in ECs; however, their functions and mechanisms in sepsis pathophysiology remain largely unclear.

4.6. ECs and COVID-19

The coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, caused a global crisis. SARS-CoV-2 infects ECs through the angiotensin-converting enzyme 2 (ACE2) receptor, leading to endothelialitis and EC dysfunction due to apoptosis and pyroptosis [102]. Systemic microvascular endothelial dysfunction arising from COVID-19 progression may result in inflammation (including cytokine storms), coagulopathy, and edema. The cytokine storm exacerbates the inflammatory symptoms in ECs, such as coagulopathy, ultimately leading to multi-organ injury [103]. Corticosteroids, IL-6 receptor antagonists, and Janus kinase (JAK) inhibitors (like baricitinib) are recommended for treating critically ill patients with COVID-19 [104,105]. A recent study revealed that IL-6 receptor

antagonists significantly improved 180-day mortality in patients with COVID-19 [106]. However, another study showed that monoclonal antibodies, including IL-6 antibodies tocilizumab and siltuximab, and the IL-1β receptor antagonist Anakinra, did not confer a significant survival benefit in patients with COVID-19 [107]. The use of an IL-6 receptor antagonist may benefit certain patients, and the dose and timing of administration need to be evaluated appropriately. Several ACE2 derivatives, including recombinant ACE2 proteins, ACE2-loaded extracellular vesicles, ACE2-mimicking antibodies, and peptide or mini-protein mimetics of ACE2, have been developed as potential SARS-CoV-2 inhibitors [108]. Complement activation exacerbates endothelial dysfunction in patients with COVID-19 [109]. Complement inhibitors, such as compstatins, Cp40/AMY-101, and eculizumab, have been shown to mitigate endothelial inflammatory damage and improve pneumonia in patients with COVID-19, thereby laying the groundwork for systematic prospective trials [110,111]. As the COVID-19 pandemic recedes, most patients have returned to their pre-infection state of health. However, a subset of patients continues to experience persistent post-infection sequelae, commonly referred to as "long COVID, " which encompasses both post-acute COVID-19 and post-COVID-19 syndrome. The prevalent symptoms of long COVID primarily consist of fatigue, shortness of breath, dyspnea, chest tightness, cough, arthralgia, headache, and cognitive dysfunction [112]. Additionally, recent studies have indicated that less than 20 % of patients were completely free of symptoms, with more than 80 % exhibiting at least one symptom. Neurocognitive long-COVID symptoms can persist for longer than one year [113–115]. Persistent glycocalyx damage and sustained T lymphocyte-associated cytokines likely account for endothelial dysfunction in patients with long-COVID-19 [116,117]. Therefore, reversing SARS-CoV-2-induced endothelial dysfunction may provide an important avenue for improving patient outcomes.

5. Future directions

Despite improvements in our understanding of the pathophysiology and treatment of severe sepsis, the associated mortality rate remains unacceptably high. Most fundamental studies have focused on isolated and specific mechanisms that underestimate the inherent complexity of host responses in the human body. Future breakthroughs require a conceptual shift emphasizing the spatially and temporally coupled networks of various cell types, inflammatory mediators, signaling pathways, transcription factors, and genes. Endothelial damage induced by sepsis is heterogeneous and the endothelium responds in ways that differ according to the nature of the pathogen, underlying comorbidities, and individual characteristics. Furthermore, there is a growing interest in monitoring endothelial function at the bedside to evaluate the pathogenesis of endothelial dysfunction, and recent studies have shown that microcirculatory alterations are closely related to organ failure [118,119]. Several endothelial biomarkers that may serve as sensitive indicators of endothelial injury have been identified. However, the use of biomarkers remains limited due to the heterogeneity of the endothelium, lack of standardization, and difficulty in continuous monitoring. Another clinical challenge that needs addressing before therapeutic interventions is the discrimination between adaptive endothelial changes and maladaptive alterations. Furthermore, diagnostic methods for assessing endothelial function at the bedside require further development. A translational gap persists between basic research and clinical trials, hindering the clinical translation of studies with positive outcomes. Therefore, mechanistically oriented clinical trials are urgently needed to demonstrate the potential benefits of protective strategies for the endothelium in patients with sepsis.

6. Limitations

This study has a few limitations. First, we used WoSCC as the only database for publication retrieval, and the publication language was limited to "English." A few valuable papers published in PubMed, Scopus, or other languages might be overlooked. Therefore, an inherent selection bias exists in the methodology. The article type was restricted to "article; " as a result, a few critical conference abstracts were not included in this study. Finally, the number of citations is influenced by numerous factors, such as the accumulation of chronology and publication platforms; thus, the number of citations does not completely correspond to their importance.

7. Conclusion

In summary, this present study provides an overview of the worldwide research status and future trends in ECs and sepsis. The most productive country, institution, author, and journal in this field are the United States, Harvard University, Bae Jong Sup, and *SHOCK*, respectively. Research on EC permeability, glycocalyx damage, biomarkers, and COVID-19 has emerged as significant topics in recent years. The protection and restoration of endothelial function provides promising prospects for managing septic complications. Further studies are warranted to validate the scope and significance of EC-oriented therapeutic strategies.

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Data availability statement

The data underlying this article are available on FigShare (https://doi.org/10.6084/m9.figshare.24634797.v1).

CRediT authorship contribution statement

Yue Shi: Writing - original draft, Formal analysis, Data curation. **Shunpan Ji:** Software, Methodology, Formal analysis. **Yuhai Xu:** Formal analysis. **Jun Ji:** Writing - review & editing. **Xiaoming Yang:** Writing - review & editing, Supervision. **Bo Ye:** Writing - review & editing. **Jingsheng Lou:** Writing - review & editing, Supervision, Methodology. **Tianzhu Tao:** Writing - review & editing, Investigation, Conceptualization.

Declaration of competing interest

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

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References

[1] B. Gyawali, K. Ramakrishna, A.S. Dhamoon, Sepsis: the Evolution in Definition, Pathophysiology, and Management, vol. 7, SAGE open medicine, 2019, 2050312119835043, https://doi.org/10.1177/2050312119835043.
[2] R.C. Bone, R.A. Balk, F.B. Cerra, R.P. Dellinger, A.M. Fein, W.A. Knaus, R.M. Schein, W.J. Sibbald, Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, Chest 101 (6) (1992) 1644–1655, https://doi.org/10.1378/chest.101.6.1644.
[3] M.M. Levy, M.P. Fink, J.C. Marshall, E. Abraham, D. Angus, D. Cook, J. Cohen, S.M. Opal, J.L. Vincent, G. Ramsay, 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference, Crit. Care Med. 31 (4) (2003 Apr) 1250–1256, https://doi.org/10.1097/01.ccm.0000050454.01978.3b.
[4] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G.R. Bernard, J.D. Chiche, C.M. Coopersmith, R.S. Hotchkiss, M.M. Levy, J.C. Marshall, G.S. Martin, S.M. Opal, G.D. Rubenfeld, T. van der Poll, J.L. Vincent, D.C. Angus, The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (8) (2016) 801–810, https://doi.org/10.1001/jama.2016.0287.
[5] K.E. Rudd, S.C. Johnson, K.M. Agesa, K.A. Shackelford, D. Tsoi, D.R. Kievlan, D.V. Colombara, K.S. Ikuta, N. Kissoon, S. Finfer, Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study, Lancet 395 (10219) (2020 Jan 18) 200–211, https://doi.org/10.1016/S0140-6736(19)32989-7.
[6] L. Evans, A. Rhodes, W. Alhazzani, M. Antonelli, C.M. Coopersmith, C. French, F.R. Machado, L. Mcintyre, M. Ostermann, H.C. Prescott, Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021, Intensive Care Med. 47 (11) (2021) 1181–1247, https://doi.org/10.1007/s00134-021-06506-y.
[7] B.D. Winters, M. Eberlein, J. Leung, D.M. Needham, P.J. Pronovost, J.E. Sevransky, Long-term mortality and quality of life in sepsis: a systematic review, Crit. Care Med. 38 (5) (2010) 1276–1283, https://doi.org/10.1097/ccm.0b013e3181d8cc1d.
[8] T.J. Iwashyna, E.W. Ely, D.M. Smith, K.M. Langa, Long-term cognitive impairment and functional disability among survivors of severe sepsis, JAMA 304 (16) (2010) 1787–1794, https://doi.org/10.1001/jama.2010.1553.
[9] E.V. Dolmatova, K. Wang, R. Mandavilli, K.K. Griendling, The effects of sepsis on endothelium and clinical implications, Cardiovasc. Res. 117 (1) (2021) 60–73, https://doi.org/10.1093/cvr/cvaa070.
[10] J. Joffre, J. Hellman, C. Ince, H. Ait-Oufella, Endothelial responses in sepsis, Am. J. Respir. Crit. Care Med. 202 (3) (2020) 361–370, https://doi.org/10.1164/rccm.201910-1911tr.
[11] J.F. Colbert, E.P. Schmidt, Endothelial and microcirculatory function and dysfunction in sepsis, Clin. Chest Med. 37 (2) (2016 Jun) 263–275, https://doi.org/10.1016/j.ccm.2016.01.009.
[12] J.E. Hirsch, An index to quantify an individual's scientific research output, Proc. Natl. Acad. Sci. USA 102 (46) (2005 Nov 15) 16569–16572, https://doi.org/10.1073/pnas.0507655102.
[13] R. Bailón-Moreno, E. Jurado-Alameda, R. Ruiz-Baños, J.P. Courtial, Bibliometric laws: empirical flaws of fit, Scientometrics 63 (2) (2005) 209–229, https://doi.org/10.1007/s11192-005-0211-5.
[14] C. Chen, L. Leydesdorff, Patterns of connections and movements in dual-map overlays: a new method of publication portfolio analysis, Journal of the association for information science and technology 65 (2) (2014) 334–351, https://doi.org/10.1002/asi.22968.
[15] J.P. Man, J.G. Weinkauf, M. Tsang, J.H.D.D. Sin, Why do some countries publish more than others? An international comparison of research funding, English proficiency and publication output in highly ranked general medical journals, Eur. J. Epidemiol. 19 (8) (2004) 811–817, https://doi.org/10.1023/b:ejep.0000036571.00320.b8.
[16] D.G. Nathan, Clinical research: perceptions, reality, and proposed solutions, JAMA 280 (16) (1998) 1427–1431, https://doi.org/10.1001/jama.280.16.1427.
[17] C. Michiels, Endothelial cell functions, J. Cell. Physiol. 196 (3) (2003 Sep) 430–443, https://doi.org/10.1002/jcp.10333.
[18] M.L. Malbrain, P.E. Marik, I. Witters, C. Cordemans, A.W. Kirkpatrick, D.J. Roberts, N. Van Regenmortel, Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice, Anaesthesiol. Intensive Ther. 46 (5) (2014) 361–380, https://doi.org/10.5603/ait.2014.0060.
[19] E. Dejana, E. Tournier-Lasserve, B.M. Weinstein, The control of vascular integrity by endothelial cell junctions: molecular basis and pathological implications, Dev. Cell 16 (2) (2009) 209–221, https://doi.org/10.1016/j.devcel.2009.01.004.
[20] D. Mehta, A.B. Malik, Signaling mechanisms regulating endothelial permeability, Physiol. Rev. 86 (1) (2006 Jan) 279–367, https://doi.org/10.1152/physrev.00012.2005.
[21] M. Radeva, J. Waschke, Mind the gap: mechanisms regulating the endothelial barrier, Acta Physiol. 222 (1) (2018), e12860, https://doi.org/10.1111/apha.12860.
[22] M.J. Allingham, J.D. van Buul, K. Burridge, ICAM-1-mediated, Src- and Pyk2-dependent vascular endothelial cadherin tyrosine phosphorylation is required for leukocyte transendothelial migration, J. Immunol. 179 (6) (2007) 4053–4064, https://doi.org/10.4049/jimmunol.179.6.4053.
[23] Y. He, X. Yuan, H. Zuo, Y. Sun, A. Feng, Berberine exerts a protective effect on gut-vascular barrier via the modulation of the Wnt/beta-catenin signaling pathway during sepsis, Cell. Physiol. Biochem. 49 (4) (2018) 1342–1351, https://doi.org/10.1159/000493412.
[24] D. Vestweber, How leukocytes cross the vascular endothelium, Nat. Rev. Immunol. 15 (11) (2015) 692–704, https://doi.org/10.1038/nri3908.
[25] C. Hwa, W.C. Aird, The history of the capillary wall: doctors, discoveries, and debates, Am. J. Physiol. Heart Circ. Physiol. 293 (5) (2007) H2667–H2679, https://doi.org/10.1152/ajpheart.00704.2007.
[26] L. Hakanpaa, E.A. Kiss, G. Jacquemet, I. Miinalainen, M. Lerche, C. Guzmán, E. Mervaala, L. Eklund, J. Ivaska, P. Saharinen, Targeting β1-integrin inhibits vascular leakage in endotoxemia, Proc. Natl. Acad. Sci. USA 115 (28) (2018) E6467–E6476, https://doi.org/10.1073/pnas.1722317115.

[27] B. Gutbier, X. Jiang, K. Dietert, C. Ehrler, J. Lienau, P. Van Slyke, H. Kim, V.C. Hoang, J.T. Maynes, D.J. Dumont, Vasculotide reduces pulmonary hyperpermeability in experimental pneumococcal pneumonia, Crit. Care 21 (1) (2017 Nov 13) 274, https://doi.org/10.1186/s13054-017-1851-6.

[28] N.C. Filewod, W.L. Lee, Inflammation without vascular leakage. Science fiction no longer? Am. J. Respir. Crit. Care Med. 200 (12) (2019) 1472–1476, https://doi.org/10.1164/rccm.201905-1011cp.

[29] C. Daly, V. Wong, E. Burova, Y. Wei, S. Zabski, J. Griffiths, K.-M. Lai, H.C. Lin, E. Ioffe, G.D. Yancopoulos, Angiopoietin-1 modulates endothelial cell function and gene expression via the transcription factor FKHR (FOXO1), Genes Dev. 18 (9) (2004) 1060–1071, https://doi.org/10.1101/gad.1189704.

[30] S. Fukuhara, K. Sako, K. Noda, J. Zhang, M. Minami, N. Mochizuki, Angiopoietin-1Tie2 receptor signaling in vascular quiescence and angiogenesis, Histol. Histopathol. 25 (3) (2010) 387–396, https://doi.org/10.14670/hh-25.387.

[31] T. Mammoto, S.M. Parikh, A. Mammoto, D. Gallagher, B. Chan, G. Mostoslavsky, D.E. Ingber, V.P. Sukhatme, Angiopoietin-1 requires p190 RhoGAP to protect against vascular leakage in vivo, J. Biol. Chem. 282 (33) (2007) 23910–23918, https://doi.org/10.1074/jbc.m702169200.

[32] T. Ziegler, J. Horstkotte, C. Schwab, V. Pfetsch, K. Weinmann, S. Dietzel, I. Rohwedder, R. Hinkel, L. Gross, S. Lee, Angiopoietin 2 mediates microvascular and hemodynamic alterations in sepsis, J. Clin. Invest. 123 (8) (2013) 3436–3445, https://doi.org/10.1172/jci66549.

[33] M.A. Titheradge, Nitric oxide in septic shock, Biochim. Biophys. Acta, Bioenerg. 1411 (2–3) (1999) 437–455, https://doi.org/10.1016/s0005-2728(99)00031-6.

[34] M.S. El-Awady, M.A. Nader, M.H. Sharawy, The inhibition of inducible nitric oxide synthase and oxidative stress by agmatine attenuates vascular dysfunction in rat acute endotoxemic model, Environ. Toxicol. Pharmacol. 55 (2017) 74–80, https://doi.org/10.1016/j.etap.2017.08.009.

[35] E. Nava, R. Palmer, S. Moncada, The role of nitric oxide in endotoxic shock: effects of NG-monomethyl-L-arginine, J. Cardiovasc. Pharmacol. 20 (1992) S132–S134, https://doi.org/10.1097/00005344-199204002-00037.

[36] K.M. Caron, O. Smithies, Extreme hydrops fetalis and cardiovascular abnormalities in mice lacking a functional Adrenomedullin gene, Proc. Natl. Acad. Sci. USA 98 (2) (2001) 615–619, https://doi.org/10.1073/pnas.98.2.615.

[37] P.-F. Laterre, P. Pickkers, G. Marx, X. Wittebole, F. Meziani, T. Dugernier, V. Huberlant, T. Schuerholz, B. François, J.-B. Lascarrou, Safety and tolerability of non-neutralizing adrenomedullin antibody adrecizumab (HAM8101) in septic shock patients: the AdrenOSS-2 phase 2a biomarker-guided trial, Intensive Care Med. 47 (2021) 1284–1294, https://doi.org/10.1007/s00134-021-06537-5.

[38] C. Geven, E. Peters, M. Schroedter, J. Struck, A. Bergmann, O. McCook, P. Radermacher, M. Kox, P. Pickkers, Effects of the humanized anti-adrenomedullin antibody adrecizumab (HAM8101) on vascular barrier function and survival in rodent models of systemic inflammation and sepsis, Shock 50 (6) (2018) 648–654, https://doi.org/10.1097/shk.0000000000001102.

[39] S. Weinbaum, J.M. Tarbell, E.R. Damiano, The structure and function of the endothelial glycocalyx layer, Annu. Rev. Biomed. Eng. 9 (2007) 121–167, https://doi.org/10.1146/annurev.bioeng.9.060906.151959.

[40] S. Reitsma, D.W. Slaaf, H. Vink, M.A. Van Zandvoort, The endothelial glycocalyx: composition, functions, and visualization, Pflueg. Arch. Eur. J. Physiol. 454 (3) (2007) 345–359, https://doi.org/10.1007/s00424-007-0212-8.

[41] L.S. Murphy, N. Wickersham, J.B. McNeil, C.M. Shaver, A.K. May, J.A. Bastarache, L.B. Ware, Endothelial glycocalyx degradation is more severe in patients with non-pulmonary sepsis compared to pulmonary sepsis and associates with risk of ARDS and other organ dysfunction, Ann. Intensive Care 7 (1) (2017) 1–9, https://doi.org/10.1186/s13613-017-0325-y.

[42] D. Chappell, M. Westphal, M. Jacob, The impact of the glycocalyx on microcirculatory oxygen distribution in critical illness, Current Opinion in Anesthesiology 22 (2) (2009) 155–162, https://doi.org/10.1097/aco.0b013e328328d1b6.

[43] E.K. Patterson, G. Cepinskas, D.D. Fraser, Endothelial glycocalyx degradation in critical illness and injury, Front. Med. 9 (2022), 898592, https://doi.org/10.3389/fmed.2022.898592.

[44] X. Li, X. Ma, The role of heparin in sepsis: much more than just an anticoagulant, Br. J. Haematol. 179 (3) (2017) 389–398, https://doi.org/10.1111/bjh.14885.

[45] A. Nelson, I. Berkestedt, A. Schmidtchen, L. Ljunggren, M. Bodelsson, Increased levels of glycosaminoglycans during septic shock: relation to mortality and the antibacterial actions of plasma, Shock 30 (6) (2008) 623–627, https://doi.org/10.1097/shk.0b013e3181777da3.

[46] E.P. Schmidt, Y. Yang, W.J. Janssen, A. Gandjeva, M.J. Perez, L. Barthel, R.L. Zemans, J.C. Bowman, D.E. Koyanagi, Z.X. Yunt, The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis, Nat. Med. 18 (8) (2012) 1217–1223, https://doi.org/10.1038/nm.2843.

[47] J.A. Sterne, S. Murthy, J.V. Diaz, A.S. Slutsky, J. Villar, D.C. Angus, D. Annane, L.C.P. Azevedo, O. Berwanger, A.B. Cavalcanti, Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis, JAMA 324 (13) (2020) 1330–1341, https://doi.org/10.1001/jama.2020.17023.

[48] T.N. Anderson, H.E. Hinson, E.N. Dewey, E.A. Rick, M.A. Schreiber, S.E. Rowell, Early tranexamic acid administration after traumatic brain injury is associated with reduced syndecan-1 and angiopoietin-2 in patients with traumatic intracranial hemorrhage, J. Head Trauma Rehabil. 35 (5) (2020) 317, https://doi.org/10.1097/htr.0000000000000619.

[49] G.B. Fields, The rebirth of matrix metalloproteinase inhibitors: moving beyond the dogma, Cells 8 (9) (2019) 984, https://doi.org/10.3390/cells8090984.

[50] J. Saoraya, L. Wongsamita, N. Srisawat, K. Musikatavorn, The effects of a limited infusion rate of fluid in the early resuscitation of sepsis on glycocalyx shedding measured by plasma syndecan-1: a randomized controlled trial, J Intensive Care 9 (1) (2021) 1, https://doi.org/10.1186/s40560-020-00515-7.

[51] L. Byrne, N.G. Obonyo, S.D. Diab, K.R. Dunster, M.R. Passmore, A.C. Boon, L.S. Hoe, S. Pedersen, M.H. Fauzi, L.P. Pimenta, F. Van Haren, C.M. Anstey, L. Cullen, J.P. Tung, K. Shekar, K. Maitland, J.F. Fraser, Unintended consequences: fluid resuscitation worsens shock in an ovine model of endotoxemia, Am. J. Respir. Crit. Care Med. 198 (8) (2018) 1043–1054, https://doi.org/10.1164/rccm.201801-0064oc.

[52] R.J. Haywood-Watson, J.B. Holcomb, E.A. Gonzalez, Z. Peng, S. Pati, P.W. Park, W. Wang, A.M. Zaske, T. Menge, R.A. Kozar, Modulation of syndecan-1 shedding after hemorrhagic shock and resuscitation, PLoS One 6 (8) (2011), e23530, https://doi.org/10.1371/journal.pone.0023530.

[53] A. Piotti, D. Novelli, J.M.T.A. Meessen, D. Ferlicca, S. Coppolecchia, A. Marino, G. Salati, M. Savioli, G. Grasselli, G. Bellani, Endothelial damage in septic shock patients as evidenced by circulating syndecan-1, sphingosine-1-phosphate and soluble VE-cadherin: a substudy of ALBIOS, Crit. Care 25 (1) (2021) 1–12, https://doi.org/10.1186/s13054-021-03545-1.

[54] E.M. Milford, M.C. Reade, Resuscitation fluid choices to preserve the endothelial glycocalyx, Crit. Care 23 (1) (2019) 1–11, https://doi.org/10.1186/s13054-019-2369-x.

[55] T. van der Poll, F.L. van de Veerdonk, B.P. Scicluna, M.G. Netea, The immunopathology of sepsis and potential therapeutic targets, Nat. Rev. Immunol. 17 (7) (2017) 407–420, https://doi.org/10.1038/nri.2017.36.

[56] H. Alsaffar, N. Martino, J.P. Garrett, A.P. Adam, Interleukin-6 promotes a sustained loss of endothelial barrier function via Janus kinase-mediated STAT3 phosphorylation and de novo protein synthesis, Am. J. Physiol. Cell Physiol. 314 (5) (2018) C589–C602, https://doi.org/10.1152/ajpcell.00235.2017.

[57] P. Lockyer, H. Mao, Q. Fan, L. Li, L.-Y. Yu-Lee, N.T. Eissa, C. Patterson, L. Xie, X. Pi, LRP1-dependent BMPER signaling regulates lipopolysaccharide-induced vascular inflammation, Arterioscler. Thromb. Vasc. Biol. 37 (8) (2017) 1524–1535, https://doi.org/10.1161/atvbaha.117.309521.

[58] S.K. Lawton, F. Xu, A. Tran, E. Wong, A. Prakash, M. Schumacher, J. Hellman, K. Wilhelmsen, N-arachidonoyl dopamine modulates acute systemic inflammation via nonhematopoietic TRPV1, J. Immunol. 199 (4) (2017) 1465–1475, https://doi.org/10.4049/jimmunol.1602151.

[59] S. Liu, Y. Dong, T. Wang, S. Zhao, K. Yang, X. Chen, C. Zheng, Vaspin inhibited proinflammatory cytokine induced activation of nuclear factor-kappa B and its downstream molecules in human endothelial EA. hy926 cells, Diabetes Res. Clin. Pract. 103 (3) (2014) 482–488, https://doi.org/10.1016/j.diabres.2013.12.002.

[60] K. Nakahira, J.A. Haspel, V.A. Rathinam, S.-J. Lee, T. Dolinay, H.C. Lam, J.A. Englert, M. Rabinovitch, M. Cernadas, H.P. Kim, Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome, Nat. Immunol. 12 (3) (2011) 222–230, https://doi.org/10.1038/ni.1980.

[61] D. Tang, R. Kang, T.V. Berghe, P. Vandenabeele, G. Kroemer, The molecular machinery of regulated cell death, Cell Res. 29 (5) (2019) 347–364, https://doi.org/10.1038/s41422-019-0164-5.

[62] Y. Sun, P. Chen, B. Zhai, M. Zhang, Y. Xiang, J. Fang, S. Xu, Y. Gao, X. Chen, X. Sui, The emerging role of ferroptosis in inflammation, Biomed. Pharmacother. 127 (2020), 110108, https://doi.org/10.1016/j.biopha.2020.110108.
[63] H. Zhao, H. Chen, M. Xiaoyin, G. Yang, Y. Hu, K. Xie, Y. Yu, Autophagy activation improves lung injury and inflammation in sepsis, Inflammation 42 (2) (2019) 426–439, https://doi.org/10.1007/s10753-018-00952-5.
[64] E. Zhang, X. Zhao, L. Zhang, N. Li, J. Yan, K. Tu, R. Yan, J. Hu, M. Zhang, D. Sun, Minocycline promotes cardiomyocyte mitochondrial autophagy and cardiomyocyte autophagy to prevent sepsis-induced cardiac dysfunction by Akt/mTOR signaling, Apoptosis 24 (3) (2019) 369–381, https://doi.org/10.1007/s10495-019-01521-3.
[65] L.G. Danielski, A.D. Giustina, S. Bonfante, T. Barichello, F. Petronilho, The NLRP3 inflammasome and its role in sepsis development, Inflammation 43 (1) (2020) 24–31, https://doi.org/10.1007/s10753-019-01124-9.
[66] T. Gong, Y. Yang, T. Jin, W. Jiang, R. Zhou, Orchestration of NLRP3 inflammasome activation by ion fluxes, Trends Immunol. 39 (5) (2018) 393–406, https://doi.org/10.1016/j.it.2018.01.009.
[67] S.B. Willingham, I.C. Allen, D.T. Bergstralh, W.J. Brickey, M.T. Huang, D.J. Taxman, J.A. Duncan, J.P. Ting, NLRP3 (NALP3, Cryopyrin) facilitates in vivo caspase-1 activation, necrosis, and HMGB1 release via inflammasome-dependent and -independent pathways, J. Immunol. 183 (3) (2009) 2008–2015, https://doi.org/10.4049/jimmunol.0900138.
[68] L.G. Danielski, A.D. Giustina, S. Bonfante, T. Barichello, F. Petronilho, The NLRP3 inflammasome and its role in sepsis development, Inflammation 43 (2020) 24–31, https://doi.org/10.1007/s10753-019-01124-9.
[69] D.C. Cornelius, O.K. Travis, R.W. Tramel, M. Borges-Rodriguez, C.H. Baik, M. Greer, C.A. Giachelli, G.A. Tardo, J.M. Williams, NLRP3 inflammasome inhibition attenuates sepsis-induced platelet activation and prevents multi-organ injury in cecal-ligation puncture, PLoS One 15 (6) (2020), e0234039, https://doi.org/10.1371/journal.pone.0234039.
[70] M. Yang, S.A. Walker, J.S. Aguilar Díaz de León, I. Davidovich, K. Broad, Y. Talmon, C.R. Borges, J. Wolfram, Extracellular vesicle glucose transporter-1 and glycan features in monocyte-endothelial inflammatory interactions, Nanomedicine 42 (2022), 102515, https://doi.org/10.1016/j.nano.2022.102515.
[71] V. Chatterjee, X. Yang, Y. Ma, B. Cha, J.E. Meegan, M. Wu, S.Y. Yuan, Endothelial microvesicles carrying Src-rich cargo impair adherens junction integrity and cytoskeleton homeostasis, Cardiovasc. Res. 116 (8) (2020) 1525–1538, https://doi.org/10.1093/cvr/cvz238.
[72] X. Wang, H. Gu, D. Qin, L. Yang, W. Huang, K. Essandoh, Y. Wang, C.C. Caldwell, T. Peng, B. Zingarelli, G.C. Fan, Exosomal miR-223 contributes to mesenchymal stem cell-elicited cardioprotection in polymicrobial sepsis, Sci. Rep. 5 (2015), 13721, https://doi.org/10.1038/srep13721.
[73] F. Tu, X. Wang, X. Zhang, T. Ha, Y. Wang, M. Fan, K. Yang, P.S. Gill, T.R. Ozment, Y. Dai, L. Liu, D.L. Williams, C. Li, Novel role of endothelial derived exosomal HSPA12B in regulating macrophage inflammatory responses in polymicrobial sepsis, Front. Immunol. 11 (2020) 825, https://doi.org/10.3389/fimmu.2020.00825.
[74] Y. Im, H. Yoo, J.Y. Lee, J. Park, G.Y. Suh, K. Jeon, Association of plasma exosomes with severity of organ failure and mortality in patients with sepsis, J. Cell Mol. Med. 24 (16) (2020) 9439–9445, https://doi.org/10.1111/jcmm.15606.
[75] S.M. Hashemian, M.H. Pourhanifeh, S. Fadaei, A.A. Velayati, H. Mirzaei, M.R. Hamblin, Non-coding RNAs and exosomes: their role in the pathogenesis of sepsis, Mol. Ther. Nucleic Acids 21 (2020) 51–74, https://doi.org/10.1016/j.omtn.2020.05.012.
[76] H. Kubo, Extracellular vesicles in lung disease, Chest 153 (1) (2018) 210–216, https://doi.org/10.1016/j.chest.2017.06.026.
[77] W. Jing, H. Wang, L. Zhan, W. Yan, Extracellular vesicles, new players in sepsis and acute respiratory distress syndrome, Front. Cell. Infect. Microbiol. 12 (2022), 853840, https://doi.org/10.3389/fcimb.2022.853840.
[78] T. Bombeli, M. Mueller, A. Haeberli, Anticoagulant properties of the vascular endothelium, Thromb. Haemostasis 77 (3) (1997) 408–423, https://doi.org/10.1055/s-0038-1655981.
[79] J.-L. Vincent, C. Ince, P. Pickkers, Endothelial dysfunction: a therapeutic target in bacterial sepsis? Expert Opin. Ther. Targets 25 (9) (2021) 733–748, https://doi.org/10.1080/14728222.2021.1988928.
[80] M. Levi, H. Ten Cate, Disseminated intravascular coagulation, N. Engl. J. Med. 341 (8) (1999) 586–592, https://doi.org/10.1056/nejm199908193410807.
[81] S.M. Opal, C.T. Esmon, Bench-to-bedside review: functional relationships between coagulation and the innate immune response and their respective roles in the pathogenesis of sepsis, Crit. Care 7 (1) (2003) 23–38, https://doi.org/10.1186/cc1854.
[82] L.L. Horstman, W. Jy, J.J. Jimenez, Y.S. Ahn, Endothelial microparticles as markers of endothelial dysfunction, Frontiers in Bioscience-Landmark 9 (2) (2004) 1118–1135, https://doi.org/10.2741/1270.
[83] E. Camerer, A.-B. Kolstø, H. Prydz, Cell biology of tissue factor, the principal initiator of blood coagulation, Thromb. Res. 81 (1) (1996) 1–41, https://doi.org/10.1016/0049-3848(95)00209-x.
[84] K. Hamilton, P. Sims, Changes in cytosolic Ca2+ associated with von Willebrand factor release in human endothelial cells exposed to histamine. Study of microcarrier cell monolayers using the fluorescent probe indo-1, J. Clin. Invest. 79 (2) (1987) 600–608, https://doi.org/10.1172/jci112853.
[85] M.V. de Wouwer, D. Collen, E.M. Conway, Thrombomodulin-protein C-EPCR system: integrated to regulate coagulation and inflammation, Arterioscler. Thromb. Vasc. Biol. 24 (8) (2004) 1374–1383, https://doi.org/10.1161/01.atv.0000134298.25489.92.
[86] C.T. Esmon, The protein C pathway, Chest 124 (3) (2003) 26S–32S, https://doi.org/10.1378/chest.124.3_suppl.26s.
[87] A.K. Ghosh, D.E. Vaughan, PAI-1 in tissue fibrosis, J. Cell. Physiol. 227 (2) (2012) 493–507, https://doi.org/10.1002/jcp.22783.
[88] S. Madoiwa, S. Nunomiya, T. Ono, Y. Shintani, T. Ohmori, J. Mimuro, Y. Sakata, Plasminogen activator inhibitor 1 promotes a poor prognosis in sepsis-induced disseminated intravascular coagulation, Int. J. Hematol. 84 (5) (2006) 398–405, https://doi.org/10.1532/ijh97.05190.
[89] C. Wu, W. Lu, Y. Zhang, G. Zhang, X. Shi, Y. Hisada, S.P. Grover, X. Zhang, L. Li, B. Xiang, Inflammasome activation triggers blood clotting and host death through pyroptosis, Immunity 50 (6) (2019) 1401–1411. e4, https://doi.org/10.1016/j.immuni.2019.04.003.
[90] C. Wang, C. Chi, L. Guo, X. Wang, L. Guo, J. Sun, B. Sun, S. Liu, X. Chang, E. Li, Heparin therapy reduces 28-day mortality in adult severe sepsis patients: a systematic review and meta-analysis, Crit. Care 18 (2014) 1–9, https://doi.org/10.1186/s13054-014-0563-4.
[91] H. Saito, I. Maruyama, S. Shimazaki, Y. Yamamoto, N. Aikawa, R. Ohno, A. Hirayama, T. Matsuda, H. Asakura, M. Nakashima, Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial, J. Thromb. Haemostasis 5 (1) (2007) 31–41, https://doi.org/10.1111/j.1538-7836.2006.02267.x.
[92] J. Kienast, M. Juers, C. Wiedermann, J. Hoffmann, H. Ostermann, R. Strauss, H.O. Keinecke, B. Warren, S. Opal, K. Investigators, Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation, J. Thromb. Haemostasis 4 (1) (2006) 90–97, https://doi.org/10.1111/j.1538-7836.2005.01697.x.
[93] J. Steppan, S. Hofer, B. Funke, T. Brenner, M. Henrich, E. Martin, J. Weitz, U. Hofmann, M.A. Weigand, Sepsis and major abdominal surgery lead to flaking of the endothelial glycocalix, J. Surg. Res. 165 (1) (2011) 136–141, https://doi.org/10.1016/j.jss.2009.04.034.
[94] R.A. Claus, C.L. Bockmeyer, U. Budde, K. Kentouche, M. Sossdorf, T. Hilberg, R. Schneppenheim, K. Reinhart, M. Bauer, F.M. Brunkhorst, Variations in the ratio between von Willebrand factor and its cleaving protease during systemic inflammation and association with severity and prognosis of organ failure, Thromb. Haemostasis 101 (2) (2009) 239–247, https://doi.org/10.1160/th08-03-0161.
[95] S.-M. Lin, Y.-M. Wang, H.-C. Lin, K.-Y. Lee, C.-D. Huang, C.-Y. Liu, C.-H. Wang, H.-P. Kuo, Serum thrombomodulin level relates to the clinical course of disseminated intravascular coagulation, multiorgan dysfunction syndrome, and mortality in patients with sepsis, Crit. Care Med. 36 (3) (2008) 683–689, https://doi.org/10.1097/ccm.0b013e31816537d8.
[96] M.A. Puskarich, D.C. Cornelius, J. Tharp, U. Nandi, A.E. Jones, Plasma syndecan-1 levels identify a cohort of patients with severe sepsis at high risk for intubation after large-volume intravenous fluid resuscitation, J. Crit. Care 36 (2016) 125–129, https://doi.org/10.1016/j.jcrc.2016.06.027.
[97] J. Saoraya, L. Wongsamita, N. Srisawat, K. Musikatavorn, Plasma syndecan-1 is associated with fluid requirements and clinical outcomes in emergency department patients with sepsis, Am. J. Emerg. Med. 42 (2021) 83–89, https://doi.org/10.1016/j.ajem.2021.01.019.
[98] R. Tian, X. Wang, T. Pan, R. Li, J. Wang, Z. Liu, E. Chen, E. Mao, R. Tan, Y. Chen, Plasma PTX3, MCP1 and Ang2 are early biomarkers to evaluate the severity of sepsis and septic shock, Scand. J. Immunol. 90 (6) (2019), e12823, https://doi.org/10.1111/sji.12823.

[99] E.J. Giamarellos-Bourboulis, A. Norrby-Teglund, V. Mylona, A. Savva, I. Tsangaris, I. Dimopoulou, M. Mouktaroudi, M. Raftogiannis, M. Georgitsi, A. Linnér, G. Adamis, A. Antonopoulou, E. Apostolidou, M. Chrisofos, C. Katsenos, I. Koutelidakis, K. Kotzampassi, G. Koratzanis, M. Koupetori, I. Kritselis, K. Lymberopoulou, K. Mandragos, A. Marioli, J. Sundén-Cullberg, A. Mega, A. Prekates, C. Routsi, C. Gogos, C.J. Treutiger, A. Armaganidis, G. Dimopoulos, Risk assessment in sepsis: a new prognostication rule by Apache II score and serum soluble urokinase plasminogen activator receptor, Crit. Care 16 (4) (2012) R149, https://doi.org/10.1186/cc11463.
[100] M.-H. Kim, J.-H. Choi, An update on sepsis biomarkers, Infection & chemotherapy 52 (1) (2020) 1, https://doi.org/10.3947/ic.2020.52.1.1.
[101] F. He, C. Zhang, Q. Huang, Long noncoding RNA nuclear enriched abundant transcript 1/miRNA-124 axis correlates with increased disease risk, elevated inflammation, deteriorative disease condition, and predicts decreased survival of sepsis, Medicine 98 (32) (2019), https://doi.org/10.1097/md.0000000000016470.
[102] Z. Varga, A.J. Flammer, P. Steiger, M. Haberecker, R. Andermatt, A.S. Zinkernagel, M.R. Mehra, R.A. Schuepbach, F. Ruschitzka, H. Moch, Endothelial cell infection and endotheliitis in COVID-19, Lancet 395 (10234) (2020 May 2) 1417–1418, https://doi.org/10.1016/S0140-6736(20)30937-5.
[103] L.A. Teuwen, V. Geldhof, A. Pasut, P. Carmeliet, COVID-19: the vasculature unleashed, Nat. Rev. Immunol. 20 (7) (2020) 389–391, https://doi.org/10.1038/s41577-020-0343-0.
[104] A. Agarwal, B. Hunt, M. Stegemann, B. Rochwerg, F. Lamontagne, R.A. Siemieniuk, T. Agoritsas, L. Askie, L. Lytvyn, Y.S. Leo, H. Macdonald, L. Zeng, A. Alhadyan, A. Muna, W. Amin, A.R.A. da Silva, D. Aryal, F.A.J. Barragan, A living WHO guideline on drugs for covid-19, BMJ 370 (2020 Sep 4) m3379, https://doi.org/10.1136/bmj.m3379.
[105] S. Noreen, I. Maqbool, A. Madni Dexamethasone, Therapeutic potential, risks, and future projection during COVID-19 pandemic, Eur. J. Pharmacol. 894 (2021 Mar 5), 173854, https://doi.org/10.1016/j.ejphar.2021.173854.
[106] S. Florescu, D. Stanciu, M. Zaharia, A. Kosa, D. Codreanu, A. Kidwai, S. Masood, C. Kaye, A. Coutts, L. MacKay, Long-term (180-day) outcomes in critically ill patients with COVID-19 in the REMAP-CAP randomized clinical trial, JAMA 329 (1) (2023) 39–51, https://doi.org/10.1001/jama.2022.23257.
[107] J. Declercq, K.F. Van Damme, E. De Leeuw, B. Maes, C. Bosteels, S.J. Tavernier, S. De Buyser, R. Colman, M. Hites, G. Verschelden, Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial, Lancet Respir. Med. 9 (12) (2021) 1427–1438, https://doi.org/10.1016/s2213-2600(21)00377-5.
[108] H. Zhang, P. Lv, J. Jiang, Y. Liu, R. Yan, S. Shu, B. Hu, H. Xiao, K. Cai, S. Yuan, Advances in developing ACE2 derivatives against SARS-CoV-2, The Lancet Microbe 4 (5) (2023 May) e369–e378, https://doi.org/10.1016/s2666-5247(23)00011-3.
[109] M. Cugno, P.L. Meroni, R. Gualtierotti, S. Griffini, E. Grovetti, A. Torri, P. Lonati, C. Grossi, M.O. Borghi, C. Novembrino, M. Boscolo, S.C. Uceda Renteria, L. Valenti, G. Lamorte, M. Manunta, D. Prati, A. Pesenti, F. Blasi, G. Costantino, A. Gori, A. Bandera, F. Tedesco, F. Peyvandi, Complement activation and endothelial perturbation parallel COVID-19 severity and activity, J. Autoimmun. 116 (2021), 102560, https://doi.org/10.1016/j.jaut.2020.102560.
[110] P. Skendros, G. Germanidis, D.C. Mastellos, C. Antoniadou, E. Gavriilidis, G. Kalopitas, A. Samakidou, A. Liontos, A. Chrysanthopoulou, M. Ntinopoulou, Complement C3 inhibition in severe COVID-19 using compstatin AMY-101, Sci. Adv. 8 (33) (2022), eabo2341, https://doi.org/10.1126/sciadv.abo2341.
[111] F. Diurno, F. Numis, G. Porta, F. Cirillo, S. Maddaluno, A. Ragozzino, P. De Negri, C. Di Gennaro, A. Pagano, E. Allegorico, Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience, Eur. Rev. Med. Pharmacol. Sci. 24 (7) (2020) 4040–4047, https://doi.org/10.26355/eurrev_202004_20875.
[112] J.B. Soriano, S. Murthy, J.C. Marshall, P. Relan, J.V. Diaz, A clinical case definition of post-COVID-19 condition by a Delphi consensus, Lancet Infect. Dis. 22 (4) (2022) e102–e107, https://doi.org/10.1016/s1473-3099(21)00703-9.
[113] V.T. Tran, R. Porcher, I. Pane, P. Ravaud, Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort, Nat. Commun. 13 (1) (2022) 1812, https://doi.org/10.1038/s41467-022-29513-z.
[114] J. Seeßle, T. Waterboer, T. Hippchen, J. Simon, M. Kirchner, A. Lim, B. Müller, U. Merle, Persistent symptoms in adult patients 1 Year after coronavirus disease 2019 (COVID-19): a prospective cohort study, Clin. Infect. Dis. 74 (7) (2022) 1191–1198, https://doi.org/10.1093/cid/ciab611.
[115] A. Carfì, R. Bernabei, F. Landi, Persistent symptoms in patients after acute COVID-19, JAMA 324 (6) (2020) 603–605, https://doi.org/10.1001/jama.2020.12603.
[116] M. Yamaoka-Tojo, Vascular endothelial glycocalyx damage in COVID-19, Int. J. Mol. Sci. 21 (24) (2020 Dec 19) 9712, https://doi.org/10.3390/ijms21249712.
[117] V. Lambadiari, A. Mitrakou, A. Kountouri, J. Thymis, K. Katogiannis, E. Korakas, C. Varlamos, I. Andreadou, M. Tsoumani, H. Triantafyllidi, A. Bamias, K. Thomas, P. Kazakou, S. Grigoropoulou, D. Kavatha, A. Antoniadou, M.A. Dimopoulos, I. Ikonomidis, Association of COVID-19 with impaired endothelial glycocalyx, vascular function and myocardial deformation 4 months after infection, Eur. J. Heart Fail. 23 (11) (2021) 1916–1926, https://doi.org/10.1002/ejhf.2326.
[118] Y. Sakr, M.-J. Dubois, D. De Backer, J. Creteur, J.-L. Vincent, Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock, Crit. Care Med. 32 (9) (2004) 1825–1831, https://doi.org/10.1097/01.ccm.0000138558.16257.3f.
[119] A. Rovas, J. Sackarnd, J. Rossaint, S. Kampmeier, H. Pavenstädt, H. Vink, P. Kümpers, Identification of novel sublingual parameters to analyze and diagnose microvascular dysfunction in sepsis: the NOSTRADAMUS study, Crit. Care 25 (2021) 1–14, https://doi.org/10.1186/s13054-021-03520-w.