Original Article

Sepsis-related immunosuppression: a bibliometric analysis

Long Jiang, Lu Wang, Daquan Zhang, Yan Liu, Dong Chen, Xiaohui Shi, Zhigao Wang, Dong Xiao

Department of Critical Care Medicine, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

Contributions: (I) Conception and design: L Jiang, D Xiao; (II) Administrative support: L Wang, D Zhang; (III) Provision of study materials or patients: Y Liu, D Chen; (IV) Collection and assembly of data: X Shi, Z Wang; (V) Data analysis and interpretation: L Jiang, D Xiao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dong Xiao. Department of Critical Care Medicine, People's Hospital of Xinjiang Uygur Autonomous Region, No. 91 Tianchi Road, Tianshan District, Urumqi 830001, China. Email: xd87654321@sina.com.

Background: Sepsis is one of the main causes of death in critically ill patients. Immunosuppression was involved deeply in the process of sepsis. The status of research on sepsis-related immunosuppression remains unclear. In this study, a bibliometric analysis was conducted to provide a preliminarily analysis of the current research status in sepsis-related immunosuppression.

Methods: The Science Citation Index Expanded (SCI-E) database in the Web of Science Core Collection was used as the data source for the literature search, and the time was set from the inception of the database to the last retrieval time for this study (i.e., May 21, 2022). Using the topic search, we searched for "sepsis" and then for "immunosuppression" in the results to obtain the final results. On the search page of the SCI-E database, we selected the document type, topic direction, MeSH topic heading, MeSH qualifier, keywords, author, journal, country, research institution, language, etc., to obtain the distribution results, and manually removed any duplicate records. We analyzed the use of keywords in the literature and the centrality of the authors, countries, and research institutions.

Results: A total of 4,132 articles were retrieved from the database over the search period of 1900 to May 21, 2022. The number of articles published increased annually. A trend of rapid growth was also observed in the number of citations. The most common topic words were humans, male, and female. The most used keywords were sepsis, immunosuppression, and male. The most published researcher was Monneret from Lyon, France. The authors of the article mainly specialized in immunology and surgery. Moldawer and Chaudry from the United States (US) had engaged in the most collaborations with other researchers. The journals that publish literature in this field are mainly journals related to critical care medicine, and the core journals included *Shock*, *Critical Care*, and *Critical Care Medicine*.

Conclusions: More and more studies are being published on sepsis-related immunosuppression and largely being conducted in developed countries. Chinese researchers need to carry out more collaborative research.

Keywords: Sepsis; immunosuppression; bibliometric analysis

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Introduction

Sepsis is an organ dysfunction caused by the uncontrolled response of the body to infection. It is one of the main causes of death in critically ill patients and seriously affects the prognosis of critically ill patients (1). In 2017, 48.9 million new sepsis cases and 11 million deaths, accounting for 19.7% of global deaths, were reported worldwide (2). Since the launch of the "Save Sepsis Campaign" in 2002, some progress has been made in both the basic and clinical research on sepsis, but the morbidity and mortality rates of sepsis have not decreased significantly (3), which may be related to immunosuppression in patients with sepsis.

Immune dysfunction is key to the occurrence and development of sepsis and is mainly manifested as an

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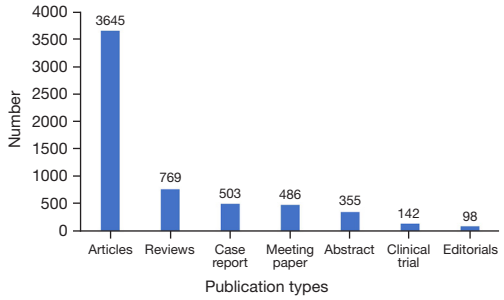

Figure 1 Publication types (top 7).

imbalance between pro-inflammatory and anti-inflammatory responses (4,5). The pro-inflammatory response can cause a storm of inflammatory factors, while the anti-inflammatory response can lead to immunosuppression. Immunosuppression is an important factor leading to the occurrence of secondary infections in the body and is also the key to poor prognosis in patients with sepsis (6,7). Some studies have highlighted the important role of the NLRP3 inflammasome in sepsis. This inflammasome regulates the activation of caspase-1 and the production and secretion of potent pro-inflammatory cytokines (8,9). The occurrence and development of immunosuppression in sepsis are mainly manifested by changes in anti-inflammatory cytokines, immune cells, and immune co-stimulatory inhibitory molecules (10-12). At present, the main clinical drugs used in this field include thymosin α1, interleukin (IL)-7, oxidized phospholipids, necrosulfanilamide and high mobility group box-1 (HMGB1) antibodies, anti-death pathway-related antibodies, and anti-programmed cell death receptor 1 (PD-1), and programmed cell death ligand 1 (PD-L1) antibodies (13-16). This study sought to conduct a preliminarily analysis of the current research status in this field through bibliometric research.

Highlight box

Key findings

- More and more studies are being published on sepsis-related immunosuppression, but the research is largely being conducted in developed countries in Europe and America. Chinese researchers need to carry out more collaborative research.

What is known and what is new?

- Sepsis is one of the main causes of death in critically ill patients. Immune dysfunction is key to the occurrence and development of sepsis.
- The number of articles on sepsis-related immunosuppression increased annually. Moldawer and Chaudry from the United States (US) had engaged in the most collaborations with other researchers. The journals that publish literature in this field are mainly journals related to critical care medicine, and the core journals included *Shock*, *Critical Care*, and *Critical Care Medicine*.

What is the implication, and what should change now?

- Chinese researchers need to carry out more collaborative research.

Methods

Literature search

Similar to other bibliometric studies (17,18), we searched the Science Citation Index Expanded (SCI-E) database in the Web of Science Core Collection, and the time was set from the inception of the database to the last retrieval time for this study (i.e., May 21, 2022). In this study, the topic search was used, and the search terms were sepsis and immunosuppression. We searched for "sepsis", and we then searched for "immunosuppression" in the previous results to obtain the final search results.

Data analysis

On the search page of SCI-E, we selected document types, topic directions, MeSH subject headings, MeSH qualifiers, keywords, authors, journals, countries, research institutions, languages, etc. to obtain the distribution results. All duplicate records were manually removed. We analyzed the use of keywords in the literature and the centrality of authors, countries, and research institutions.

Statistical analysis

This study mainly describes the current status of research on sepsis and immunosuppression, and the data are expressed in numbers and percentages (n, %).

Results

General information

A total of 4,132 articles were identified in the search of the database over the search period of 1900 to May 21, 2022. These articles cited a total of 81,267 references, including 2,023 self-citations. At the time of our analysis, these articles have been cited 114,138 times, with an average of 27.62 citations per article and an H-index of 139. The types of documents included articles, reviews, case reports, meeting papers, abstracts, clinical trials, and editorials (*Figure 1*), of

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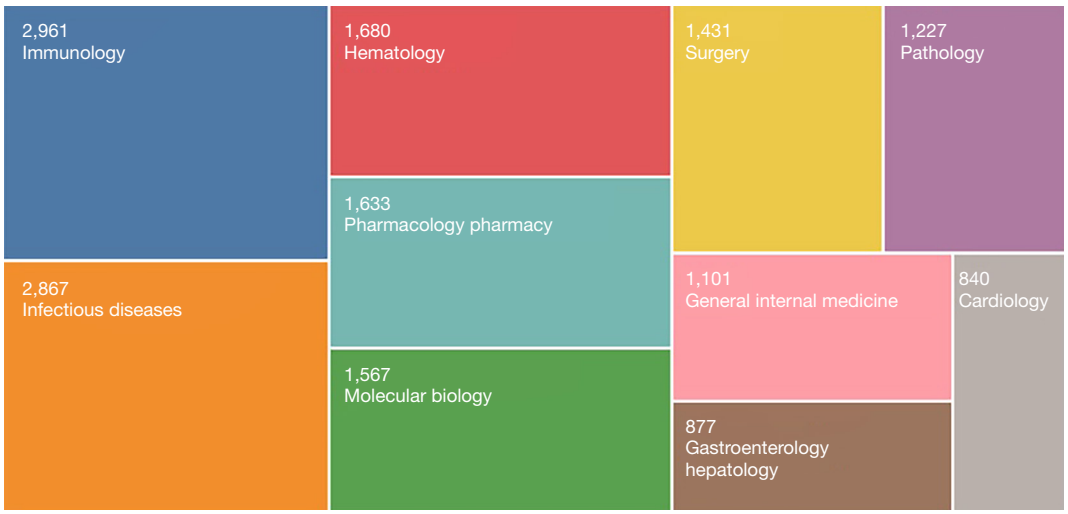

Figure 2 Top 10 directions in publications.

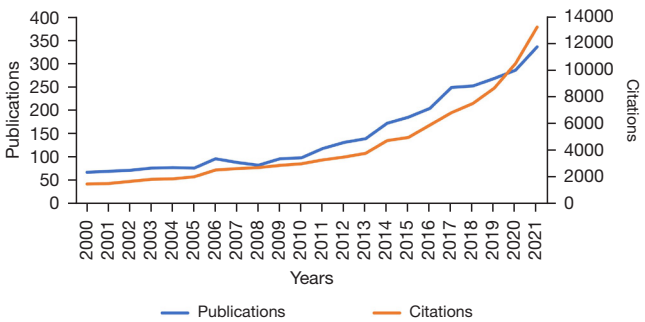

Figure 3 Annual changes in publications and citations.

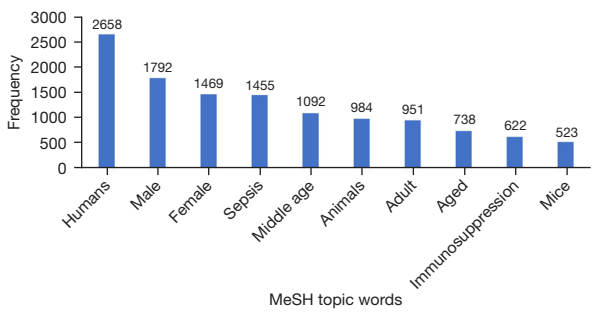

Figure 4 Top 10 MeSH topic words.

which articles represented the largest number. However, in some instances, the same article had multiple classifications. In addition to clinical trials being classified as original articles, some systematic reviews, conference papers, and case reports were also classified as original articles. In terms of topic classification, any given article may have also been classified as being associated with multiple disciplines; however, the most common topics were immunology and infectious disease (*Figure 2*). According to the annual analysis, there was an obvious trend whereby the number of articles published increased year by year (*Figure 3*). A trend of rapid growth was also observed in the number of citations (*Figure 3*).

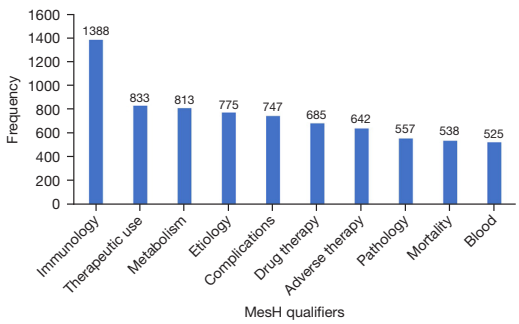

Figure 5 Top 10 MeSH qualifiers.

Topic words and qualifiers

The analysis of the MeSH subject headings recorded in these documents revealed that the most used topic heading was "Human", followed by "Male", and "Female" (*Figure 4*). The results of the MeSH qualifier analysis showed that the most used MeSH qualifier was "Immunology", followed by "Therapeutic use", and "Metabolism" (*Figure 5*).

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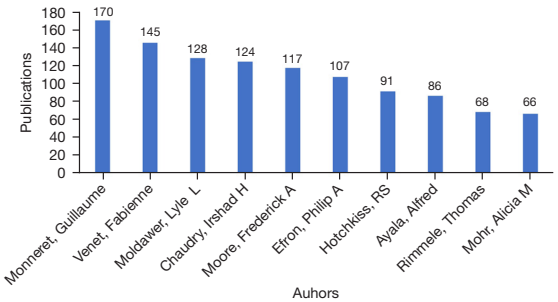

Figure 6 Top 10 authors in terms of the number of publications.

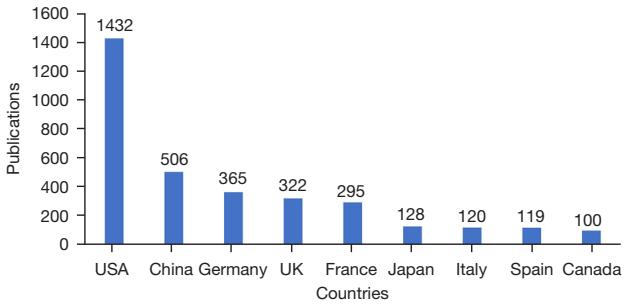

Figure 8 Top 9 countries in terms of publications.

Table 1 Centrality of authors

Rank	Authors	Specialty	Centrality
1	Moldawer, Lyle L	Surgery	0.46
2	Chaudry, Irshad H	Surgery	0.39
3	Monneret, Guillaume	Immunology	0.37
4	Venet, Fabienne	Immunology	0.33
5	Moore, Frederick A	Surgery	0.27
6	Efron, Philip A	Surgery	0.23
7	Hotchkiss, RS	Anesthesiology	0.20
8	Ayala, Alfred	Surgery	0.16
9	Rimmele, Thomas	Anesthesiology	0.11
10	Mohr, Alicia M	Surgery	0.10

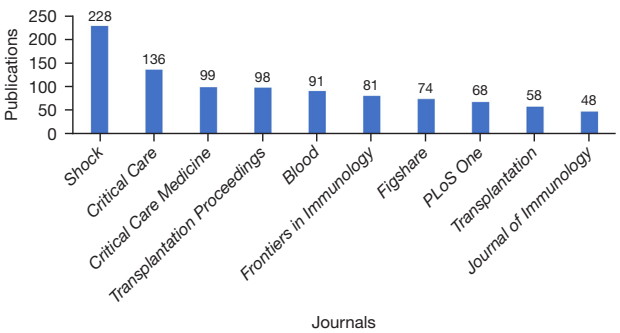

Figure 7 Top 10 journals in terms of the number of publications.

Authors

In the research field of sepsis-related immunosuppression, the author with the most published papers was Monneret from Lyon, France, who specializes in immunology and the pathophysiology of injury-induced immunosuppression, followed by Venet, a colleague of Monneret, and Moldawer from the University of Florida College of Medicine in the United States (US), who specializes in surgery (*Figure 6*). A further analysis showed that the main specialized areas of the researchers were surgery, followed by anesthesia, and immunology, which were also related to the disciplinary settings of different countries and research institutions (*Table 1*). The results of the centrality analysis showed that an author's centrality had a certain relationship with the number of published documents, but it was not the author with the largest number who had the highest centrality score. In this field, Moldawer from the University of Florida College of Medicine, US, had the highest centrality score, followed by Chaudry from the University of Alabama, Birmingham, US.

Journals

The results of the analysis of the journals (*Figure 7*) revealed that most of the articles in this field had been published in critical care-related journals, such as *Shock*, *Critical Care*, and *Critical Care Medicine*. According to Bradford's law, the core journals in the field are *Shock*, *Critical Care*, *Critical Care Medicine*, *Transplantation Proceedings*, and *Blood* and *Frontiers in Immunology*.

Countries, institutions, and languages

In this research field, the top 3 countries with the most published papers were the US, China and Germany (*Figure 8*). However, in the centrality ranking of countries, the top 3 countries were the US, the United Kingdom (UK), and Germany; China was only ranked 7th (*Table 2*). The institutions with the most published papers were the League of European Research Universities (LERU) and Udice

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Table 2 Centrality of countries

Rank	Countries	Centrality
1	US	0.26
2	UK	0.20
3	Germany	0.18
4	France	0.15
5	Italy	0.14
6	Japan	0.11
7	China	0.10
8	Spain	0.09
9	Canada	0.08

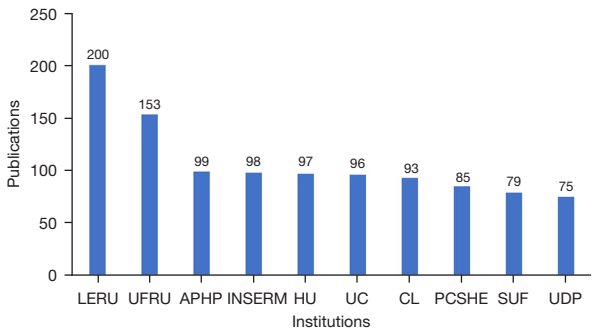

Figure 9 Top 10 institutions in terms of publications. LERU, League of European Research Universities; UFRU, Udice French Research Universities; APHP, Assistance Publique Hopitaux Paris; INSERM, Institut National De La Sante Et De La Recherche MedicalE; HU, Harvard University; UC, University of California System; CL, Chu Lyon; PCSHE, Pennsylvania Commonwealth System of Higher Education; SUF, State University System of Florida; UDP, Universite De Paris.

French Research Universities (UFRU). The 3rd and 10th institutions were France and the US, respectively, while Chinese research institutions did not enter the top 10 (*Figure 9*). The results of the centrality ranking of institutions (*Table 3*) showed that LERU, INSERM, and UFRU held the 1st to 3rd places, respectively, but there was still no institution in China whose centrality score ranked in the top 10. In terms of the language of publication, in the SCI database, research in this field was dominated by English-language articles (92.9%), followed by Chinese-language articles (2.59%) (*Table 4*), and a small amount of German-, French-, and Spanish-language articles.

Table 3 Centrality of institutions

Rank	Institutions	Centrality
1	LERU	0.34
2	INSERM	0.29
3	UFRU	0.25
4	HU	0.22
5	APHP	0.19
6	UC	0.16
7	SUF	0.12
8	PCSHE	0.11
9	UDP	0.10

LERU, League of European Research Universities; UFRU, Udice French Research Universities; APHP, Assistance Publique Hopitaux Paris; INSERM, Institut National De La Sante Et De La Recherche MedicalE; HU, Harvard University; UC, University of California System; CL, Chu Lyon; PCSHE, Pennsylvania Commonwealth System of Higher Education; SUF, State University System of Florida; UDP, Universite De Paris.

Table 4 Publications in different languages (top 10)

Language	Publications	% of 4,132
English	3,805	92.09
Chinese	107	2.59
German	97	2.35
French	55	1.33
Spanish	55	1.33
Japanese	15	0.36
Portuguese	14	0.34
Russian	14	0.34
Italian	12	0.29
Polish	9	0.22

Keywords

The use of keywords was analyzed, and the results showed (*Figure 10*) that sepsis and immunosuppression were the most commonly used keywords, while male, female, and elderly were also frequently used keywords. Additionally, infection, septic shock, and inflammation were also commonly used keywords. The results of the centrality analysis (*Table 5*) showed that the top 3 key words with the highest centrality scores were sepsis, immunosuppression, and infection.

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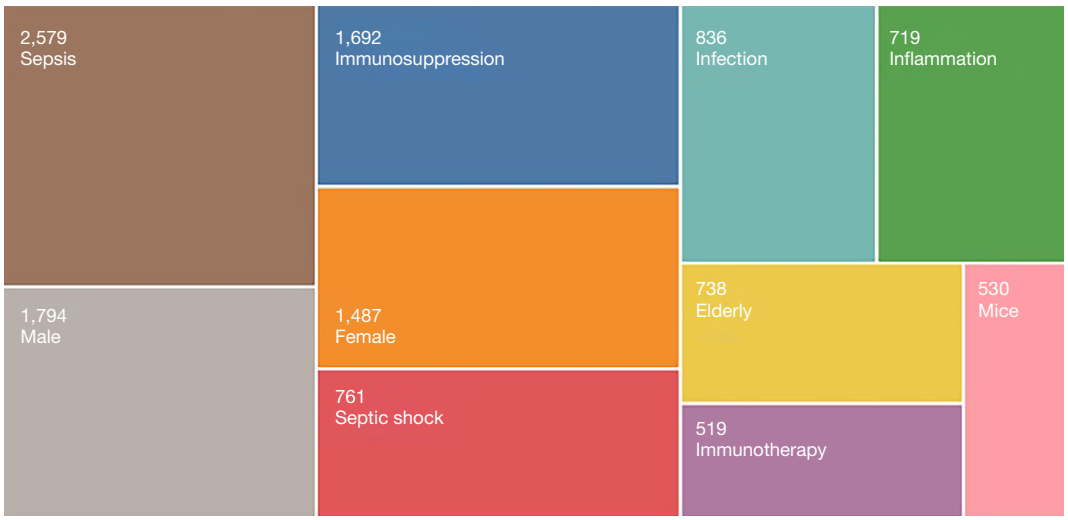

Figure 10 The top 10 most used keywords in the articles on sepsis and immunosuppression.

Table 5 Centrality of keywords

Rank	Keywords	Centrality
1	Sepsis	0.41
2	Immunosuppression	0.33
3	Infection	0.26
4	Inflammation	0.23
5	Male	0.17
6	Female	0.15
7	Septic shock	0.14
8	Immunotherapy	0.12
9	Mechanism	0.11
10	Elderly	0.10

Discussion

In this study, we searched for articles published from 1900 to May 21, 2022 and retrieved a total of 4,132 articles. These articles largely reflect the research profile of sepsis-related immunosuppression. Our findings showed that the research literature in this field is dominated by original articles, followed by some reviews and case reports. The number of documents published has increased year by year, especially after 2013. There were some differences between the results of the subject word analysis and the keyword analysis. The most used subject words were humans, male, and female, while the most used keywords were sepsis, immunosuppression, and male, and the most used MeSH qualifiers were immunology, therapeutic use, and metabolism. An analysis of the authors showed that the most published researcher was Monneret from Lyon, France. The authors of the articles largely specialized in immunology and surgery. In terms of research cooperation, Moldawer and Chaudry from the US had engaged in the most cooperation with other researchers. In relation to the analysis of journals, the results showed that the journals publishing articles in this field were mainly journals related to critical care medicine, and the core journals included *Shock*, *Critical Care*, and *Critical Care Medicine*. In terms of the distribution of countries, most of the researchers came from the US, China, and Germany, but the countries with the most cooperation were the US, the UK, and Germany. In terms of research institutions, the institutions were largely based in Europe and the US. The articles in this field were mainly published in the English language.

At present, research in the field of sepsis-related immunosuppression has generated abundant results and made significant progress (19-21). It is currently thought that sepsis-related immunosuppression mainly involves the innate and adaptive immune systems and is manifested by an increased release of anti-inflammatory cytokines, the apoptosis of immune cells, the decreased expression of human leukocyte antigen DR (HLA-DR), pyroptosis, and the increased expression of PD-1 and PD-L1 (4,22,23).

Anti-inflammatory cytokines mainly include IL-4, IL-10, and IL-37. IL-4 is produced and secreted by activated T cells and mast cells, induces cluster of differentiation (CD)4$^+$

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T cells to differentiate into helper T cells 2 (Th2 cells), and promotes self-secretion through positive feedback, while stimulating the release of other anti-inflammatory cytokines, and exerts the biological effect of inhibiting the release of pro-inflammatory cytokines (24). Furthermore, sepsis-related immunosuppression has been proved to be involved in the occurrence of sepsis-associated encephalopathy through multiple pro-inflammatory cytokines (25). Also, this kind of immunosuppression is associated with the neuron dysfunction and final cell death (26).

IL-10 is mainly secreted by mononuclear macrophages and Th2 cells, which can inhibit T cell proliferation and immune effector function, inhibit the release of pro-inflammatory cytokines, and promote the proliferation of immune-suppression cells, including regulatory T cells and bone marrow-derived suppressor cells (27,28). A previous study has shown that IL-10 inhibits the proliferation of T cells in patients with sepsis, reduces the secretion of effector cytokines, and at the same time, promotes the proliferation of regulatory T cells and has an immunosuppressive effect (29).

IL-37, which is a unique member of the IL-1 cytokine family, is also an inhibitor of immune responses and inflammation. It is produced by immune and non-immune cells and inhibits pro-inflammatory cytokine release and antigen presentation (30). Another study found that the expression of IL-37 in patients with sepsis is significantly increased, which can inhibit the proliferation and release of pro-inflammatory cytokines and is closely related to the severity of the inflammatory response (31). Another study showed that IL-37 significantly downregulates the expression of major histocompatibility complex class II molecules and CD86 in septic mice, and inhibits antigen presentation, indicating that IL-37 has immunosuppressive effects in sepsis (32).

Apoptosis refers to the autonomous and orderly death of cells controlled by genes to maintain the stability of the internal environment. There are 2 main types of apoptosis pathways in sepsis; that is, the exogenous and endogenous pathways. In the exogenous pathway, caspase-8 is first activated through the Fas/Fas ligand pathway, and caspase-3 is then activated to exert the biological effect of apoptosis (33). In the endogenous pathway, cytochrome C and caspase activator 1 first form a multimer. Caspase-9 is activated through combination with the multimer to form apoptotic bodies, and finally activates caspase-3, thus generating biological effects in apoptosis. The endogenous pathway, regulated by members of the B-cell lymphoma/leukemia-2 (Bcl-2) family, accelerates apoptosis through the pro-apoptotic protein Bim, while inhibiting apoptosis through anti-apoptotic proteins, such as Bcl-2 (34,35). A previous study found that the expression levels of cytochrome C, Bim, caspase-3, caspase-8, caspase-9, etc. in the sepsis mouse model were significantly increased, while the expression level of Bcl-2 was significantly decreased, which promoted T cell apoptosis (36).

HLA-DR is a major histocompatibility complex class II molecule, which is mainly expressed in monocytes natural killer cells, macrophages, and other innate immune cells, and acquired immune cells, including B lymphocytes and activated T lymphocytes (37). A study by Zhuang *et al.* has shown that HLA-DR is a good indicator for evaluating the immune status of patients with sepsis and is closely related to a poor clinical prognosis (38). It is currently believed that an HLA-DR level below 30% indicates the existence of immunosuppression (39). Winkler *et al.* confirmed that the HLA-DR level of patients diagnosed with sepsis in the intensive care unit was 70% lower than that of uninfected preoperative patients, and the HLA-DR level was negatively correlated with the sequential organ failure scores of patients (39). Zhuang *et al.* found that HLA-DR levels in sepsis patients were negatively correlated with a poor clinical prognosis and immunosuppression (38). Zhou *et al.* demonstrated that HLA-DR levels were significantly reduced in mice undergoing sepsis compared to sham-operated mice (40).

Pyroptosis is a type of programmed cell death characterized by loss of plasma membrane integrity, cell swelling and rupture, followed by the efflux of intracellular substances and the activation of an inflammatory response. The pyroptosis of immune cells in sepsis mainly exerts biological effects through classical and non-canonical pathways (41). Among them, the classical pathway activates caspase-1 through the inflammasome. Conversely, activated caspase-1 promotes the expression of inflammatory factors (e.g., IL-1β, and IL-18) and HMGB1, recruits inflammatory cells to aggregate, and expands the inflammatory response. However, it cleaves to and activates gasdermin D, which translocates to the cell membrane to form holes, resulting in cell pyroptosis. The non-canonical pathway binds to caspase-4, caspase-5, and caspase-11 through bacterial lipopolysaccharide, activates caspase-1 and gasdermin D, and leads to pyroptosis (42).

A previous study showed that the expression level of caspase-1, the percentage of apoptosis in the peripheral blood mononuclear cells induced by caspase-1, and the level of IL-18 were significantly higher in patients with post-

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traumatic sepsis than healthy subjects, and the percentage of monocyte apoptosis predicted the occurrence of post-traumatic sepsis (43). PD-1 is a type I transmembrane glycoprotein that is mainly expressed in activated T cells and B cells. The combination of PD-1 on the surface of T cells and PD-L1 on the surface of antigen-presenting cells can lead to T cell exhaustion, which is mainly manifested as weakened effector T cell function, decreased cytokine secretion, and inhibited cell proliferation. Increases in the expression of PD-1 suggest that the clinical prognosis of patients with sepsis is poor (15). The increased expression of PD-1 on the surface of T cells in patients with sepsis has been shown to inhibit the secretion of cytokines, such as tumor necrosis factor (TNF)-α, while the administration of a PD-1 antibody has been shown to promote the release of TNF-α (15). Shao *et al.* found that PD-1 expression in T cells of patients with septic shock is associated with a poor clinical prognosis and was an independent risk factor for 28-day all-cause mortality (44). Patera *et al.* found that the expression levels of PD-1 and PD-L1 in neutrophils and monocytes in patients with septic shock were significantly higher than those in patients without infection in the intensive care unit, and PD-1, PD-L1 expression levels were positively correlated with the severity of sepsis and mortality (45).

At present, the treatment of sepsis is mainly based on standard protocols, such as early fluid resuscitation, antibiotic use, and organ support according to the Sepsis-3 guidelines (1). However, strict adherence to standard regimens has not significantly reduced the mortality rate of patients with sepsis (1). Based on clinical understandings of the importance of sepsis-induced immunosuppression in organ damage and death and knowledge of the effects of anti-inflammatory cytokines, immune cell apoptosis, and negative co-stimulatory molecules in patients with sepsis, the use of immunotherapy in the treatment of sepsis has gradually received attention. Combined immunotherapy has achieved initial results in sepsis patients, and has shown great potential and development space. It is expected to become a new treatment strategy in the future and bring a breakthrough in the treatment of sepsis (46).

According to the results of this study, the current research is mainly published in English and mainly occurs in developed countries in Europe and the US, and the participants are mainly immunology-related researchers. We recommend that more clinicians specializing in critical care medicine participate in research in this field, conduct in-depth testing, observe sepsis patients in clinical practice, and carefully evaluate the immune system and functional status of patients. At the same time, various researchers, research institutions, and even countries should cooperate fully and work together to solve the problem of sepsis-related immunosuppression. According to our findings, we believe that the one research hotspot of sepsis in the future might be the immunotherapy in septic patients. As for cooperation, we recommend that Chinese investigators adopt more multicenter clinical research, or conduct more related research with investigators from other different disciplines.

This study had some limitations. First, this study was a bibliometric study, which mainly analyzed the research status of sepsis-related immunosuppression from macroscopic statistical indicators, and an in-depth analysis of each article was not conducted. Second, as each literature may have obvious inconsistencies in the classification of topic headings and the use of keywords, the results of this study may be biased and not reflect the actual situation. Third, this study used the SCI database. This database covers most of the current major medical research journals; however, there are still some journals in other languages that were not included in this study, and thus some important journals may have been missed. We suggest that the SCI database include journals in languages other than English as much as possible to provide more adequate data sources for bibliometric research.

Conclusions

There are many literatures published on sepsis-related immunosuppression, but the research is relatively center in developed countries in Europe and America. There is lack of cooperation among Chinese researchers in this field.

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Footnote

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-300/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-300/coif). The authors have no conflicts of interest to declare.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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