Bibliometric study of sepsis-associated liver injury from 2000 to 2023

Zhang Z et al. Sepsis-associated liver injury

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Abstract

BACKGROUND
Sepsis-associated liver injury (SLI) is a severe and prevalent complication of sepsis.

AIM
This research intended to explore the literature on SLI via a bibliometric approach.

METHODS
Reviews and articles correlated with SLI published from Jan 1, 2000 to Oct 28, 2023 were searched from the Web of Science Core Collection. Then, the searched data were analyzed using VOSviewer, CiteSpace, and R language.

RESULTS
There were 787 publications involved in this paper, comprising 745 articles and 42 reviews. China, the USA, and Germany are the primary publication sources in this area. Studies related to SLI primarily focused on mechanisms of pathogenesis, as evidenced by analyzing keywords, references, and the counting of original research. These studies mainly involved tumor necrosis factor alpha, inflammation, oxidative stress, and nuclear factor-kappa B.
CONCLUSION

There is significant growth in the research on SLI. Current investigations primarily involve basic experiments that aimed at uncovering pathogenic mechanisms. According to the analyzed literature, the identified pathogenic mechanisms and potential therapeutic targets serve as the foundation for translating findings from basic research to clinical applications.

**Key Words:** sepsis; liver injury; bibliometric analysis; cite space; VOS viewer

**Core Tip:** NLRP3 inflammasome is the most recent keyword exhibiting the most significant citation bursts. The revelation of pathogenic mechanisms and potential therapeutic targets serves as the basis for translating from basic research to clinical application. In conclusion, our research will offer a helpful reference for subsequent studies on SLI.

INTRODUCTION

Sepsis, a condition marked by life-threatening organ dysfunction resulting from an aberrant host response to infection[1], has become a principal contributor to global health loss. According to a global epidemiological survey, there were 48.9 million incident sepsis cases registered and 11.0 million sepsis-associated deaths issued, which accounted for 19.7% of global mortality in 2017[2]. During systemic infections, the liver serves as both a host response target and an inflammatory process regulator[3]. The incidence of sepsis-associated liver injury (SLI) ranges from 34% to 46%, which is lower than in other organs due to the liver's high regenerative capacity[4-6]. However, SLI is connected with severe sepsis complications. SLI patients’ mortality ranges from 54% to 68%, which is higher relative to the mortality rate in sepsis sufferers with respiratory system dysfunction[7-9]. Given the dangers of SLI, it has become a high-profile area of research. Over the past two decades, a substantial number of studies on SLI have been
published, mainly addressing epidemiology, pathogenic mechanisms, etc. Despite the marked growth in the number of studies, the pathogenesis of SLI is not fully understood. Moreover, effective and targeted strategies for the treatment of SLI remain limited in clinical practice. Consequently, analysis of the current status, focus areas and future prospects is significant to improve our understanding of SLI.

Bibliometrics refers to the analysis of published information and its associated metadata, employing statistics to elucidate or illustrate relationships between published works[10]. Bibliometrics employs mathematical approaches to overcome the space and time limitations, allowing scholars to gain a comprehensive understanding of the current status, key points, and tendency in a specific study field. Nowadays, bibliometric analysis is widely utilized in the medical field, comprising areas such as lung cancer, heart failure, and pneumonia[7,11,12].

To the best of the author's knowledge, a bibliometric analysis of SLI has not yet been undertaken. Consequently, our objective was to comprehensively screen publications related to SLI and utilize bibliometrics to disclose development proclivities and primary discoveries in this field.

MATERIALS AND METHODS

Data sources and search strategies
The Web of Science Core Collection (WoSCC) database was recruited for literature search. The query terms were shown as follows: Topic search = “liver injury” OR “liver damage” OR “hepatic injury” OR “hepatic damage” AND sepsis OR septic. Upon confining the language to English and publication types to reviews and articles, 1314 papers issued from Jan 1, 2000 to Oct 28, 2023 were searched from WoSCC. The abstracts and titles were independently screened by two reviewers to eliminate literature not pertinent to SLI. After reading the full text, a total of 787 publications specifically focusing on SLI were included (Figure 1).

Data analysis
The publications with complete datasets and cited references were obtained from Web of Science CC for subsequent analysis. Bibliometric visualization was conducted using CiteSpace (version 6.1. R6) and VOSviewer (version 1.6.19). Each node in the collaborative network map denoted a distinct element, including journals, countries, and authors. The centrality was signified by a purple ring around a node, indicating the node's importance and its significant impact in this field. The lines connecting nodes denoted cooperative alliances between institutions or countries, with thicker lines representing stronger cooperation. The SLI's yearly publications and the institutions' total publications were presented via a line graph. The R language was employed to draw the world map, illustrating the publications of different countries. The reference citation analysis (RCA) system was adopted to analyze the impact index of publications. The RCA system was accessible via the following uniform resource locator: https://www.referencecitationanalysis.com/.

RESULTS

Publication output

The number of publications in different periods provided insight into the level of research interest in SLI, indicating the speed and development of this field. After screening, 787 publications were included, comprising 745 articles (94.46%) and 42 reviews (5.54%). The research output on SLI from 2000 to 2023 was shown in Figure 2, which could be categorized as stable growth (2000–2017), accelerated growth (2018–2019), and a flourishing period (2020–2023). Of note, the total number of publications for 2023 was not counted, as data extraction was finalized on October 28, 2023. Even so, 58 relevant publications were still identified in 2023. A large number of papers were released between 2020 and 2023, demonstrating a burgeoning interest in the field in recent years.

Country analysis
In total, 56 countries contributed related articles and reviews in this field. These countries’ distributions were depicted in Figure 3A, where the number and color depth indicated the publications’ number in different countries. To a certain degree, the quantity of publications across various states represented the level of interest in SLI within those regions. Referring to Figure 3B, the top ten countries, ranked based on the publications’ number, were concentrated in Asia (China, Japan, South Korea and Turkey, $n = 477$), the North American (the United stated, $n = 171$), Europe (Germany, the United Kingdom, Sweden and Netherland, $n = 128$) and Africa (Egypt, $n = 18$). Among these countries, China held the top spot with 358 publications, accounting for over one-third of the publications’ total number. In addition, Citespace Software was adopted to construct and visualize the country collaboration network (Figure 3C). Each node represented a country. The green ring represented the related publications from a specific year, and its size corresponded to the number of publications. Nodes encircled by purple rings exhibited significant centrality (centrality $\geq 0.01$), suggesting their high influence and importance. Countries with higher publication counts, including the USA, China, the UK and Germany were identified by purple rings and multiple layers of green, demonstrating their sustained research attention and significant role in the SLI development throughout the period. Of note, Malaysia occupied the top five in centrality with only 2 publications, suggesting that quantity was not the only criterion for judging the impact of papers. Besides, the collaboration network showed that China, the USA and Germany, as the top three countries with regard to the publications’ quantity, had communication with most countries.

**Institutional analysis**

Between 2000 and 2023, 500 institutions carried out research on SLI. The top 10 institutions that published related papers were shown in Figure 4A. The Shanghai Jiao Tong University (19 publications), the Huazhong University of Science and Technology (18 publications), and Southern Medical University (17 publications) ranked as the top three academies by the number of publications, demonstrating their great impact and
broad interest in this sphere. Academies from China accounted for eight of the ten most productive institutions, indicating a high level of attention from Chinese researchers to this field. The centrality was ranked in Table 1, showing that the influence of institutions in this field did not vary significantly. An institutional collaboration network was established via CiteSpace, with the minimum publication count per agency set to 10. Besides, significant cooperation had been constructed among various institutions worldwide (Figure 4B). The Shanghai Jiao Tong University with the largest number of publications had established communication with 19 other institutions, such as Fudan University, Nanjing university, and Shandong University.

**Journal analysis**

The top 10 journals ranked by publication count were shown in Table 2. Shock (IF = 3.1) was the most active journal in SLI, with 44 publications, succeeded by Journal of Surgical Research (IF = 2.2), with 23 publications; International Immunopharmacology (IF = 5.6), with 21 publications; Frontiers in Pharmacology (IF = 5.6), with 17 publications; Frontiers in Immunology (IF = 7.3), with 15 publications; Critical Care Medicine (IF = 8.8), with 14 publications; Experimental and Therapeutic medicine (IF = 2.7), with 11 publications; American Journal of Physiology-Gastrointestinal and Liver Physiology (IF = 4.5), with 10 publications; Biomedicine & Pharmacotherapy (IF = 7.5), with 10 publications; Journal of Hepatology (IF = 25.7), with 10 publications. SHOCK, the most widely published journal in the field of SLI, is dedicated to publishing documents in the areas of clinical and basic researches of ischemia, inflammation, sepsis, trauma, shock, and related pathobiological states. The top 10 co-cited journals were presented in Table 2. The top three rankings were Critical Care Medicine with 1093 co-citations, Shock with 978 co-citations, and Hepatology with 898 co-citations, respectively. According to co-citation analysis, Critical Care Medicine held significant influence in the field of SLI. The relationship between 388 identified journals, each with more than 15 citations, was illustrated in Figure 5A. The citation links within the field of SLI were visualized in Figure 5B. The scattered dots on the left represented citing
journals, the scattered dots on the right represented cited journals, and the colors
distinguished the disciplines to which the journals belonged. A thicker citation link
represented a closer alignment in research content between the journals where the
research was published or cited. As exhibited in Figure 5B, the citing papers in
immunology, biology and molecular fields (yellow citation link) were most closely
associated with cited papers from molecular areas, biology, and genetics, health,
nursing and medicine.

Top 10 co-cited and cited publications
The top 10 cited publications, consisting of six articles and four reviews, were shown in
Table 3. All six articles were basic studies focusing on the molecular mechanisms and
potential treatment targets of SLI. Role of G-protein-coupled adenosine receptors in
downregulation of inflammation and protection from tissue damage (Akio Ohta et al., 2001)
was the most frequently cited article in the field of SLI. It established the critical role of
A2a adenosine receptors in the physiological negative feedback mechanism that limited
and terminated tissue-specific and systemic inflammatory responses, including SLI. The
top 10 co-cited publications were listed in Table 4, with two of them surpassing 100 co-
citations. One of these two articles was The Third International Consensus Definitions for
Sepsis and Septic Shock (Sepsis-3) (Mervyn et al., 2016). In this literature, authors provided
an updated definition and clinical criteria for sepsis, including Sequential Organ Failure
Assessment (SOFA) score for investigating the function of organ such as liver. The other
of these two articles was a review published in 2014 entitled The role of the liver in sepsis.
This review summarized clinical outcomes in SLI invalids, discussed the function of
liver injury in promoting sepsis, and described the hepatic immune response’ crucial
role in managing sepsis and homeostasis progression. Burst detection was used to
determine which journals attracted significant attention over a specified period. In
Figure 6, the top 20 publications with the most significant citation bursts were
presented, illustrating the different focuses of researcher over time. As the most co-cited
reference, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3),
also exhibited the strongest citation bursts. The research by Angus et al. received widespread citations from 2004 to 2006, focusing on the epidemiology of severe sepsis and SLI. However, another study conducted by Gong et al., widely cited from 2020 to 2023, indicated the key effect of gut microbiota in SLI and the hepatoprotective effect of granisetron in the development of sepsis.

**Top 10 publications in impact index**

In bibliometric research, publication impact index rankings could help to find the latest highlight articles. The top 10 publications in impact index based on RCA were shown in Table 6, consisting of eight articles and two reviews. Both reviews were related to the gut-liver axis, which had been identified as a potential target for therapeutic intervention. All eight articles were related to the treatment of SLI, indicating that this topic remained of great interest to researchers. Two of the articles investigated the protective effects of granisetron and the herbal formula BaWeiBaiDuSan in SLI through the gut-liver axis, respectively. Besides, six articles reported that other molecules played a protective role in SLI, including CD39, 6-Gingerol, YAP1, obeticholic acid, PPARγ, and resveratrol. In addition to the gut-liver axis, these articles also mentioned other potential therapeutic targets, including P2X7 receptor inflammatory signaling pathway, Nrf2 pathway, ferroptosis resistance, ATF4-mediated autophagy activity, ROS/TXNIP/NLRP3 signaling pathway, and SIRT1-mediated HMGB1 nucleocytoplasmic translocation pathway.

**Author analysis**

The embraced 787 documents included 4314 authors, and Table 5 presented the top 10 authors based on the number of publications. Thiemermann, Christoph was the most prolific author, with 14 publications that accumulated 444 citations, averaging 31.7 citations per publication. Additionally, the top 10 authors predominantly came from China (4) and the United States (2). The top 10 authors by total link strength were displayed in Table 5. Vollmar, Brigittewas was the predominant author in the field of
SLI (total link strength = 1600 times). Our analysis showed that the rankings of total link strength and publications were inconsistent for the same author, suggesting that the number of publications did not entirely capture the author’s influence in the corresponding field. Co-citation referred to instances where references, journals, or authors from multiple papers were cited together via another paper. A total of 154 authors, each co-cited no less than 10 times, were selected for co-citation author visualization. As shown in Figure 7, five clusters were identified, with the largest comprising 62 authors, and the others containing 47, 20, 16, and 9 authors, respectively.

**Keywords analysis**

Keywords typically reflect the research theme, and a comprehensive keyword analysis indicates the current study trend in a certain area. As shown in Table 7, the top 20 most cited keywords were sepsis, liver injury, gene expression, tumor necrosis factor alpha (TNF-α), inflammation, rat, activation, oxidative stress, nuclear factor-kappa B (NF-κB), nitric oxide, CLP (cecal ligation and puncture), Kupffer cell, cell, inhibition, apoptosis, mechanism, dysfunction, LPS (lipopolysaccharide), mortality, and liver. The top two keywords, “sepsis” and “liver injury”, were cited over 300 times, and six other keywords were cited more than 100 times. Analysis of these keywords revealed that the research hotspots on the mechanism of SLI mainly involved oxidative stress, inflammation, TNF-α, NF-κB, and Kupffer cell, etc. Besides, research methods used in SLI included rat models, cell studies, LPS, and CLP, etc. CiteSpace was used to analyze keywords. As shown in Figure 8A, the node size represented the keywords’ frequency, while the lines represented their correlations. The keywords (top 20) exhibiting the largest citation bursts were illustrated in Figure 8B. The top-ranked keyword “TNF-α” remained a research focus from 2000 to 2007, suggesting the key role of TNF-α in the mechanism of SLI based on earlier studies. Between 2019 and 2023, the keywords showing the strongest citation bursts were pathway (2019–2023), autophagy (2019–2023), dysfunction (2020–2021), and NLRP3 inflammasome 2020–2023). This suggested that additional mechanisms contributing to SLI were being discovered.
DISCUSSION

We performed a bibliometric study to review the worldwide advancements in research related to SLI from 2000 to 2023. Our analysis indicated that SLI-related research had generally trended upwards since 2000. Currently, SLI has emerged as a significant research area in the field of sepsis.

Out of the 56 countries that published SLI-related studies, China contributed to over one-third of the total publications, indicating a strong interest among Chinese scholars in the field of SLI. However, the United States ranked first in centrality, indicating its significant influence in the field. Notably, Malaysia ranked fourth in centrality even though it only participated in two studies related to SLI. One of these two studies demonstrated that simvastatin attenuated hepatic inflammatory injury through the NF-κB/p6/survivin signaling pathway in an LPS experimental model. Such results may support the statins' clinical use to prevent liver injury in sepsis, although further clinical studies are necessary[13]. Another of these two studies suggested that carbamazepine may protect against septic liver injury by fully activating autophagy[14]. These two studies provided potential therapeutic targets for the treatment of SLI and therefore had greater impact.

In the analysis of journals, Critical Care Medicine was the most co-cited journal, which had been identified as one of the top journals for sepsis. Shock, Critical Care Medicine, and Journal of Hepatology ranked in the top for both the publication number and co-citation frequency, indicating that substantial amounts of high-quality papers were published in these three journals. As demonstrated in the journals' dual-map overlay, the journals mainly focused on immunology, molecular, and genetics.

Within the top 10 cited periodicals, the majority uncovered mechanisms and potential therapeutic targets of SLI through basic studies. Burst detection analysis of references could help to identify research hotspots over time. Of the publications with citation bursts from 2020 to 2023, only one was an article, and the rest were reviews. The research described in this article was considered as a focus of attention in recent years.
In this article, researchers established the gut microbiota as an upstream controller in liver injury triggered by polymicrobial sepsis and identified granisetron as an anti-inflammatory compound, providing a novel therapeutic approach for SLI[15]. It is noting that findings mentioned above have been limited to animal models. Despite the discovery of a number of pathogenic mechanisms and therapeutic targets for SLI, there is still a lack of high-quality clinical trials to validate these potential treatments.

Keywords can provide a succinct description of an paper's subject and are extensively utilized for publication retrieval and literature classification[16]. Most of the top 20 keywords could be divided into two categories. One category is in the early years of research (2000-2010), the primary focus was on understanding the fundamental mechanisms and pathways involved in SLI. Key cited keywords from this period include TNF-α, inflammation, oxidative stress, NF-κB and nitric oxide. TNF-α and NF-κB are the two most common molecules implicated in the pathogenesis of SLI. Generated via monocytes and macrophages in the process of acute inflammatory response, TNF-α is a cytokine related to inflammation, which can induce cell necrosis or apoptosis through diverse intracellular signaling mechanisms[17]. In the pathogenesis of sepsis, TNF-α released by Kupffer cells can activate immune cells and release a range of downstream inflammatory mediators through the activation of specific transmembrane TNF receptors, resulting in liver injury[3]. NF-κB, a significant intracellular nuclear transcription factor, is involved in a wide range of diseases, comprising Alzheimer's disease, glioblastoma, and acute respiratory distress syndrome[18-20]. It can be triggered by LPS to enter the nucleus and function as a transcription factor to regulate transcription of various genes encoding pro-inflammatory cytokines, adhesion molecules and chemokines[21]. Hence, NF-κB signaling is the most important signaling pathway to trigger the inflammatory cascade in sepsis[22]. The other category is that of recent years (2011-2023), where research has shifted to basic experimental research rather than clinical research. Strongly cited keywords during this period include rat, LPS, CLP, and NLRP3 inflammasome. LPS, an essential component of the Gram-negative bacteria outer membrane, significantly
affects sepsis through the innate immune system over-activation[23]. Consequently, intraperitoneal injection of LPS is one of the common methods to induce SLE model in rats[24]. Another classic method is CLP. This procedure involves ligating below the ileocecal valve post-midline laparotomy, accompanied by puncturing the cecum with a needle[25]. Since the cecum serves as the bacterial contamination’ endogenous cause, its perforation leads to bacterial peritonitis and subsequent mixed enteric bacteria translocation into the bloodstream. In an experimental setting, the CLP model is viewed as a realistic model for studying the underlying mechanisms of SLE[26].

The keyword NLRP3 inflammasome currently has the strongest citation bursts. The NLRP3 inflammasome assembles as a protein complex responding to cellular perturbations. This process results in the caspase-1 activation, promoting inflammatory cytokines’ release and maturation, involving interleukin (IL)-18 and IL-1β, and resulting in inflammatory cell death (pyroptosis)[27]. NLRP3 inflammasome is connected to diverse diseases, containing metabolic disorders, multiple sclerosis and inflammatory bowel disease[28-30]. In sepsis, excessive inflammasome activation and pyroptosis are associated with liver injury[31]. Therefore, blocking NLRP3 activation in different ways can attenuate sepsis-induced acute liver injury and may increase survival. For instance, silencing the NLRP3 gene 48 hours before inducing sepsis results in improved hyperbilirubinemia and reduced neutrophil infiltration in hepatic tissue[32]. Compared to silencing NLRP3 gene, inhibition of NLRP3 activation by drugs is more clinically feasible. Currently, several drugs have been shown to attenuate SLE by inhibiting NLRP3 inflammasome, such as cinnamomum osmophloeum, theaflavin, and Prim-O-glucosylcimifugin[33-35].

There are several limitations to our study. First, we only included the publications indexed in the WoSCC database, making it possible that certain momentous publications indexed in other databases were overlooked. Second, only English documents were enrolled. Third, we completed the literature search on October 28, 2023, which may have missed some of the literature published in 2023.
CONCLUSION
This study provides general characteristics of SLI research, including institutions, countries, journals, authors, keywords and references. Briefly, the total trend in publications from 2000 to 2023 has been upward. China, the USA, and Germany are the top three nations regarding the publication number. The three main contributing institutions are Shanghai Jiao Tong University, Huazhong University of Science and Technology, and Southern Medical University. The top three co-cited journals are Critical Care Medicine, Shock, and Hepatology. The most recent keyword showing the strongest citation bursts is NLRP3 inflammasome. The findings of pathogenic mechanisms and potential therapeutic targets serve as the basis for translating from basic research to clinical application. Collectively, our research is expected to tender a beneficial reference for future exploration to SLI.
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