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Research Landscape on COVID-19 and Liver Dysfunction: A Bibliometric Analysis

Zyoud S COVID-19 and liver dysfunction

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Abstract

BACKGROUND

The global spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), responsible for coronavirus illness 2019 (COVID-19), poses a significant risk to public health. Beyond the respiratory issues initially associated with the condition, severe cases of COVID-19 can also lead to complications in other organs, including the liver. Patients with severe COVID-19 may exhibit various clinical signs of liver dysfunction, ranging from minor elevations in liver enzymes without symptoms to more serious cases of impaired liver function. Liver damage is more commonly observed in patients with severe or critical forms of the disease.

AIM

The objective of this study was to present the research landscape on COVID-19 and liver dysfunction while also offering valuable insights into the prominent areas of interest within this particular domain.

METHODS

On February 18th, 2023, Scopus was utilized to conduct a comprehensive exploration of the relationship between COVID-19 and the liver. The investigation encompassed the

period from January 1, 2020, to December 31, 2022. Primary sources were meticulously examined and organized in a Microsoft Excel 2013 spreadsheet, categorized by journal, institution, funding agency, country, and citation type. To explore the prominent topics and knowledge network related to the subject, VOSviewer version 1.6.18 was employed.

RESULTS

There were 2336 publications on COVID-19 and liver dysfunction analysed in this study, of which 558 were published in 2020, 891 in 2021, and 887 in 2022. Researchers from 111 different countries participated in the retrieved documents. The United States had the highest number of participating studies, with 497 documents, representing 21.28% of the total, followed by China with 393 documents (16.82%) and Italy with 255 documents (10.92%). In the context of research related to COVID-19 and the liver, cooccurrence analysis has identified three distinct clusters of topics: (1) the first group, titled 'COVID-19 vaccines in liver transplant recipients'; (2) the second cluster, titled 'liver function tests as a predictor of the severity and clinical outcomes in hospitalized patients'; and (3) the third cluster, titled 'care of patients with liver disease during the COVID-19 pandemic.'

CONCLUSION

This bibliometric study provides a comprehensive overview of liver-related publications in COVID-19 research over the past three years. The study highlights the significant contributions of high-income nations, particularly the United States, China, and Italy, to the production of liver-related scholarly literature in this field. Most of the articles focused on liver dysfunction in COVID-19 patients and the implications of the virus for gastroenterologists and hepatologists.

Key Words: COVID-19; bibliometric; Scopus; VOSviewer; liver

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Core Tip: Severe cases of COVID-19 can lead to liver dysfunction, and this study provides a comprehensive overview of liver-related publications in COVID-19 research. The findings highlight the significant contributions of high-income countries, such as the United States, China, and Italy, to the production of liver-related scholarly literature in this field. The research clusters identified in the study focus on COVID-19 vaccines in liver transplant recipients, liver function tests as predictors of severity and clinical outcomes in hospitalized patients, and the care of patients with liver disease during the COVID-19 pandemic.

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) has had a large worldwide impact. There have been over 765 million confirmed cases and nearly 6.92 million fatalities as of May 3, 2023 [1]. COVID-19 symptoms range from modest respiratory difficulties to severe respiratory distress syndrome, which can lead to organ failure and death. Older people with preexisting health issues are especially vulnerable. It is crucial to mention that in addition to its effects on the lungs, COVID-19 can cause liver damage [2-6]. COVID-19-related liver injury is defined as any liver damage that occurs in people who have COVID-19, regardless of whether they have a preexisting liver ailment [7-11]. Severe COVID-19 infections can cause liver damage through a variety of mechanisms, including immune-mediated damage, ischemic hepatitis caused by a systemic inflammatory response, drug-induced liver injury, reactivation of preexisting chronic liver disease, and direct cytopathic effects from the virus replicating in hepatocytes [12-15].

The effects of COVID-19-induced liver dysfunction on prognosis and symptoms [16-20]. Because there is no cure for COVID-19-induced liver damage, treatment is only supportive. Preexisting liver diseases and nutritional support can help identify and

treat liver disorders ^[21]. COVID-19 and liver dysfunction are evolving, but quantitative and visual studies based on bibliometrics are insufficient. This chasm stifles field research. COVID-19 and liver dysfunction research is visualized in this bibliometric analysis. Scopus data are analysed by VOSviewer for citations, terms, and clusters. This analysis will identify research hotspots for COVID-19 and liver dysfunction, as well as historical trends and future directions.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted on 18 February 2023 using a bibliometric methodology.

Bibliographic database

The Scopus database was chosen as the source of data for this study for various reasons. First, Scopus stands out as the largest scientific database when compared to alternatives such as Web of Science. Second, it offers convenient options for exporting and analysing data, and it is compatible with Microsoft Excel and visualization tools. Third, Scopus is a comprehensive database that encompasses citations from diverse fields, including social and health disciplines. This aspect holds significance because research on detention and deportation spans multiple scientific domains. Consequently, Scopus emerged as the most appropriate choice for conducting the present study ^[22-24].

Search strategies

The search was limited to publications between January 1, 2020, and December 31, 2022, and the search strategy involved three steps.

In the **first step**, terms related to COVID-19 were selected from the Medical subject headings (MeSH) of PubMed and previous studies related to COVID-19 ^[25-29]. Next, the retrieved terms were entered into the Scopus engine as "Article Title/Abstract" to retrieve publications related to COVID-19.

In the **second step**, the publications obtained in the first step were filtered to include only those with "liver and related words" in their title. Keywords relevant to the liver were

selected from the previous liver and COVID-19 meta-analyses [30-34] and were entered into the Scopus engine to retrieve publications related to the liver.

Then, in the third step, publications that were published as an erratum were excluded.

The final search query used for data extraction from Scopus looked like this: (TITLE-ABS("COVID 19") OR TITLE-ABS("2019 novel coronavirus") OR TITLE-ABS("novel coronavirus") OR TITLE-ABS("coronavirus 2019") OR TITLE-ABS("*novel CoV") OR TITLE-ABS("coronavirus disease 2019") OR TITLE-ABS("2019-novel CoV") OR TITLE-ABS("Wuhan coronavirus") OR TITLE-ABS("2019 ncov") OR TITLE-ABS("Wuhan pneumonia") OR TITLE-ABS("COVID 2019") OR TITLE-ABS(COVID19) OR TITLE-ABS(*COVID*) OR TITLE-ABS(nCoV) OR TITLE-ABS("corona virus 2019") OR TITLE-ABS("nCoV-2019") OR TITLE-ABS(nCoV2019) OR TITLE-ABS("nCoV 2019") OR TITLE-ABS(2019-ncov) OR TITLE-ABS(COVID-19) OR TITLE-ABS("Severe acute respiratory syndrome coronavirus 2") OR TITLE-ABS("SARS Coronavirus 2") OR TITLE-ABS("SARS-CoV-2") OR TITLE-ABS("SARS-CoV 2")) AND (TITLE(liver) OR TITLE(Hepati*) OR TITLE(aminotransferase) OR TITLE(bilirubin) OR TITLE(prothrombin) OR TITLE(ALT) OR TITLE(AST) OR TITLE(Hepato*) OR TITLE(Cirrhosis)) AND (LIMIT-TO (PUBYEAR,2022) OR LIMIT-TO (PUBYEAR,2021) OR LIMIT-TO (PUBYEAR,2020)) AND (EXCLUDE (DOCTYPE,"er"))

During every stage of the search process, quotation marks were employed to accurately retrieve the specific phrase. Moreover, the use of asterisk truncation acted as a flexible wildcard, enabling the retrieval of any possible term.

Validation of the search strategy

Indeed, limiting the search to the title of publications in the Scopus database can improve the accuracy of retrieved data by reducing the number of false positive results. By focusing the search on the title, the search algorithm will only retrieve articles with "liver" in their titles, meaning that irrelevant articles that may mention "liver" in their abstracts or full texts will not be retrieved. As mentioned, this approach may slightly reduce the level of sensitivity, meaning that some relevant articles that do not have a "liver" in their titles may be missed [35, 36]. The study employed a validated research

approach to ensure dependable and precise findings. To minimize the risk of false positive results, documents with even numbers (15, 30, 45, 60, *etc.*) up to the end of the retrieved documents list were carefully assessed by evaluating their titles and abstracts. The research strategy underwent continuous refinement until an entirely accurate collection of randomly selected outcomes was obtained. To confirm the absence of false negative results or missed findings, the research productivity of twenty active authors in the field was analysed. A Spearman correlation test was utilized to compare the results derived from the research strategy with those from the authors. The study revealed a strong and statistically significant correlation ($p < 0.001$; $r = 0.953$) between the two sets of findings, underscoring the research strategy's high level of validity. Importantly, Sweileh, and Zyoud had previously employed this validation approach [37-39].

Bibliometric analysis

The data collected included the following bibliometric parameters: the types of documents (such as articles, books, or conference proceedings), the year of publication, the number of publications, the citation count (which indicates how many times other works have cited the publication), the country where the publication originated, the institution or organization that produced the publication, and the journals where the publications appeared. The *Impact Index Per Article* displayed represents the highest-cited papers, specifically the top 10, and is derived from the *Reference Citation Analysis* (RCA) database. RCA is an open citation analysis database covering various fields and is owned by Baishideng Publishing Group Inc., situated in Pleasanton, CA 94566, USA [40-42].

Visualize analysis

For bibliometric visualization, the software VOSviewer (version 1.6.18, Leiden University, Leiden, The Netherlands) was used [43]. In scientific research, the use of VOSviewer software for bibliometric visualization and term co-occurrence analysis is widespread. By identifying patterns of international collaboration and analysing the cooccurrence of terms in the titles and abstracts of publications, researchers can gain

insight into the hottest topics in a particular field and track scientific progress [43]. Using VOSviewer software, a network of terms illustrates the relationship between terms according to the number of publications they appear together. This enables researchers to identify clusters of related terms that represent particular research areas or trending topics. As a result, researchers can better understand the current state of research in a particular field and identify areas for future study by identifying hot topics [44, 45]. These data can be used to guide funding decisions, identify possible collaborators, and inform policy decisions.

RESULTS

General characteristics of the retrieved articles

A total of 2,336 publications on COVID-19 and liver dysfunction were analysed in this study. Among them, 558 were published in 2020, 891 in 2021, and 887 in 2022. Regarding the types of publications, 1,438 (61.56%) were articles, 417 (17.85%) were letters, 357 (15.28%) were reviews, and 124 (5.31%) fell under other categories, such as editorials and notes.

Top ten active countries

Researchers from 111 different countries participated in the retrieved documents. The United States had the highest number of participants in the research, with 497 documents, representing 21.28% of the total. China followed closely behind with 393 documents, representing 16.82% of the total, and Italy came third with 255 documents, representing 10.92% of the total publications on research related to COVID-19 and liver dysfunction. Table 1 lists the top ten active countries, of which the top 10 countries represented 84.63% of all articles published. Figure 1 is a network visualization map showing the collaboration between countries regarding coauthorship. The minimum inclusion threshold was set at 30 documents per country, and a total of 22 countries met this threshold. In the visualization, each country is represented by a circle, and the size of the circle indicates the level of contribution the country has made in terms of coauthorship. Lines represent the links between countries, and the thickness of the line

indicates the strength of collaboration between the two countries. According to the centrality measures used in the map, the United States appears to be the most central country in terms of collaborations, followed by China and Italy.

Analysis of institutions

Eight thousand six hundred forty institutions participated in research in this field, of which the top 10 institutions represented 15.97% of all published articles. INSERM contributed the most articles ($n = 26$, 5.49%), followed by Imperial College London ($n = 23$, 4.85%) and Sorbonne Université ($n = 21$, 4.43%) (Table 2).

Journal analysis

The top ten most productive journals in research related to COVID-19 and the liver are shown in Table 3. Approximately 19.91% of the articles were published on this list. The *Journal of Hepatology* published the most articles ($n = 85$, 3.64%), followed by *Liver International* ($n = 64$, 2.74%) and the *World Journal of Gastroenterology* ($n = 62$, 2.65%).

Analysis of citations

The documents retrieved had a total of 30,766 citations, a mean of 13.17, and an h -index of 75. A total of 638 (27.3%) documents had no citations, while 55 had 100 or more citations. The top ten articles, ranked by the number of citations, collectively received 4,758 citations. The citations for these publications varied from 283 to 1,126 in total [13, 46-54] (Table 4). The range of the impact index per article varied from 88.7 to 394.7 among the top 10 most cited articles.

Term co-occurrence cluster analysis of research hotspots

In the context of COVID-19 and liver research, co-occurrence analysis was used to identify the most commonly used terms in the titles and abstracts of relevant articles. In this case, VOSviewer was used to create a bubble map, which represents each term as a bubble, and the bubble size indicates the frequency of occurrence of that term. The analysis identified 172 terms that occurred at least 50 times in the titles and abstracts of the included publications. The bubbles are grouped into clusters based on the similarity of their cooccurrence patterns. There are three different groups: (1) the blue cluster, which is named 'COVID-19 vaccines in liver transplant recipients'; (2) the red group,

which is titled "liver function tests as a predictor of COVID-19 severity and clinical outcomes of COVID-19 in hospitalized patients"; and (3) the green group, which is titled "care of patients with liver disease during the COVID-19 pandemic".

DISCUSSION

The correlation between liver injury and COVID-19 has been found to be associated with the severity and mortality of the disease. These findings strongly indicate a relationship between liver injury and COVID-19. However, despite the observation that severe and fatal cases of the disease primarily affect elderly individuals with liver injury, the specific underlying mechanisms remain unclear [55].

The findings indicate that the United States, China, and Italy have been actively involved in COVID-19 and liver dysfunction research and have produced many publications on the subject. Nemours studies on the productivity of COVID-19 research in various fields [56-60], as measured by publications, found that the United States, China, and Italy were the leading producers of COVID-19 publications during this period of time. The United States and China have dominated research output in numerous fields, including the health sciences [61, 62]. According to a report released by Japan's Science and Technology Ministry, China has emerged as the global frontrunner in scientific research output, surpassing the United States in both overall volume and the number of impactful studies. The report, published by Japan's National Institute of Science and Technology Policy (NISTP), reveals that China now leads the world in annual scientific research paper publications, followed by the United States and Germany [63]. There are several factors that contribute to both the United States and China being leaders in scientific research. These factors include the size of their economies, the significant amount of money invested in R&D, and the large number of researchers working across various fields [64, 65]. Notably, both countries have allocated significant funds to healthcare and biotechnology [61, 65-67], ensuring that researchers have the resources they need to conduct thorough studies that yield reliable results. Furthermore, both countries have large and diverse scientific communities that encourage interdisciplinary

research and expert collaboration. Funding also plays a pivotal role in driving research output, as researchers studying COVID-19 and liver dysfunction in both countries can seek substantial grants. These grants provide the necessary resources to pursue ambitious research projects and attract top talent, addressing critical health issues. Notable organizations such as the National Natural Science Foundation of China [68-70], the National Institutes of Health [71, 72], and Gilead Sciences [47, 73] offer sizable grants for researchers studying COVID-19 and liver dysfunction in the United States and China, respectively.

One of the key hot topics in the current study was 'COVID-19 vaccines in liver transplant recipients'. Solid organ transplant recipients face a significant risk of death from COVID-19, with mortality rates ranging from 13% to 39% [74, 75]. As a result, many countries have given priority to vaccinating this vulnerable group using mRNA vaccines. Nonetheless, there is limited information available regarding their response to vaccination and its effectiveness [76]. It is critical that liver transplant recipients receive the COVID-19 vaccine to avoid hospitalization and serious illness. COVID-19 vaccines have been shown in studies to be safe and effective in people who have had liver transplants. It should be noted, however, that these vaccines may not elicit as strong an immune response as in healthy individuals [77]. As a result, liver transplant recipients should consult their healthcare provider about the best time to get vaccinated, taking into account their specific immunosuppression regimens and recent transplant surgeries [78]. Patients who have had a liver transplant should talk to their doctor about whether they need more vaccine doses or a different vaccine to maximize their immune response [79].

'Liver function tests as a predictor of COVID-19 severity and clinical outcomes in hospitalized patients' is another study topic. Liver function tests (LFTs) are regularly conducted in hospitalized COVID-19 patients to assess disease severity and likelihood of poor clinical outcomes [80]. COVID-19 causes liver inflammation and abnormal LFTs [81]. LFT, COVID-19 severity, and clinical outcomes have been studied [7-11]. In 2022, a study in the World Journal of Gastroenterology reported that abnormal levels of

aspartate aminotransferase (AST) and total bilirubin (T-Bil) were associated with higher mortality rates than other liver damage indicators during hospitalization. Vasopressor medications and mechanical ventilation were linked to abnormal AST, T-Bil, and ALP levels. Thus, COVID-19 patients often have abnormal liver chemistries upon hospital admission, which can predict their severity and prognosis. Healthcare practitioners can assess risk and predict the need for advanced treatment for these individuals by measuring ALT, AST, ALP, and T-Bil [82]. COVID-19 individuals with abnormal LFTs may also have prior liver disease, medication toxicity, or bacterial or viral coinfection. Thus, LFTs should be included with other clinical and laboratory data when predicting severity and clinical outcomes [83, 84].

The treatment of liver disease has become increasingly important during the COVID-19 epidemic. Individuals with liver disease are more vulnerable to COVID-19-related severe illness and mortality due to factors such as a compromised immune system, advanced age, and underlying health conditions [85]. Given this scenario, patients must carefully prioritize pandemic preparedness measures. Any deviation from their treatment plan, missed appointments, or delayed therapy can aggravate their liver disease and increase their COVID-19 risks [86]. Individuals with liver disease should therefore take COVID-19 precautions such as frequent and thorough handwashing, avoiding large crowds, and wearing face masks [87]. Adopting a healthy lifestyle is also important for strengthening their immune systems and preventing COVID-19 complications. This includes regular exercise, a balanced diet, abstaining from alcohol and smoking, and getting enough sleep [88, 89].

Strengths and limitations

Although this is the first bibliometric analysis to assess worldwide research output in the field of COVID-19 and liver, according to previous similar studies, this study had several limitations, and it is essential to acknowledge them to ensure transparency and promote further research in the field. Some limitations that could have affected this bibliometric analysis of COVID-19 and liver research output worldwide may include the following. First, Scopus is a widely used database for bibliometric analyses, and its

coverage of peer-reviewed literature is generally comprehensive. However, the bibliometric analysis may not capture all the relevant COVID-19 and liver research publications because not all journals are indexed in Scopus, and some of the relevant publications may have been published in nonindexed or non-English language journals. Second, using MeSH terms in the title of the publication is a common practice in bibliometric analysis to ensure the accuracy and relevance of the search results. However, including some publications that use related terms in other document parts may be a mistake. Therefore, it is recommended to use a combination of search terms, including title, abstract, and keywords, to increase the sensitivity of the search. However, if these false-negative results occur in the current study, they will have little effect on the overall results. Third, the analysis may not account for the quality of the publications, as it only counts the number of publications without assessing their impact, significance, or credibility. Furthermore, the ranking of publications based on total citations rather than annual citation averages could have excluded some recently published high-quality publications. However, this does not undermine these publications' importance or contribution to the field. It is essential to note that the limitations identified in this bibliometric analysis could affect the precision and completeness of the results obtained. However, the limitations highlighted by the authors do not significantly compromise the study's validity.

CONCLUSION

This bibliometric study provides a comprehensive overview of liver-related publications in COVID-19 research over the past three years. The study highlights the significant contributions of high-income nations, particularly the United States, China, and Italy, to producing liver-related scholarly literature in this field. Most of the articles focused on liver dysfunction in COVID-19 patients and the implications of the virus for gastroenterologists and hepatologists. Although the study acknowledges the importance of abnormal liver function tests in COVID-19, it also identifies knowledge gaps about their pathophysiology and prognostic value. The study indicates that well-

designed prospective studies with specific research questions can be used to fill in these gaps and further investigate the topic. This bibliometric analysis provides a solid foundation for future research on liver injury and treatment for COVID-19. The findings of this study can be used by decision-makers or researchers to prioritize research areas and allocate resources for enhancing our understanding of the impact of COVID-19 on liver function.

ARTICLE HIGHLIGHTS

Research background

Abnormal liver chemistry findings are commonly observed in individuals with COVID-19. As a result, there is a significant body of literature comprising published clinical studies that specifically examine the implications of hepatic involvement in COVID-19.

Research motivation

Understanding the current state of research and hotspots in the field of COVID-19 and liver dysfunction is crucial for identifying knowledge gaps and informing future research directions.

Research objectives

The purpose of this study is to present a comprehensive overview of the existing research on COVID-19 and liver dysfunction through the utilization of bibliometric analysis.

Research methods

A thorough and validated search query was conducted using the SciVerse Scopus database to identify relevant publications on the topic of COVID-19 and liver dysfunction. Subsequently, the research hotspots in related fields were examined using VOSviewer software.

Research results

Three distinct clusters of topics were identified: COVID-19 vaccines in liver transplant recipients, liver function tests² as predictors of severity and clinical outcomes in hospitalized patients, and the care of patients with liver disease during the COVID-19 pandemic.

Research conclusions

The first bibliometric analysis is presented here, which is represented by the study and offers valuable insights into the research landscape on COVID-19 and liver dysfunction. Valuable reference can be derived from the findings in this field by scholars, as a comprehensive summary is provided and the frontiers of research related to COVID-19 and liver dysfunction are identified.

¹

Research perspectives

The goal of this study is to have current areas of focus within the field of COVID-19 and liver dysfunction identified, which can help future research be guided and clinical practice be informed. By using bibliometric analysis, a comprehensive overview of the literature on this topic is provided by the study, and the latest developments in the field can be kept up-to-date by researchers and clinicians.

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SIMILARITY INDEX

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