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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Biologic therapy for Crohn's disease over the last 3 decades

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Abstract

BACKGROUND

Despite the overload of publications on Crohn's disease (CD), no comprehensive analysis of biologic therapy for CD has been reported.

AIM

To determine knowledge gaps and identify areas of interest of biologic therapy for CD.

METHODS

The top 100 highest-cited original articles were identified from January 1991 to December 2020 in the Clarivate Analytics Web of Science Core Collection database. We conducted a bibliometric analysis of biologic therapy for CD based on total citations, summarized the bibliographic information of the articles related to CD biologic therapy, and explored the research hotspots.

RESULTS

The top 100 highest-cited original articles were identified with total citations ranging from 307 to 2978. The 2000s (Period II, $n = 66$) yielded the most influential original articles and saw the most dramatic growth. Among the top 10 countries, including 8 European countries and 2 North American countries, the United States ($n = 37$) and Belgium ($n = 20$) contributed the most publications. Among the top 10 institutions, the University Hospital Gasthuisberg in Belgium ($n = 23$), the University of Chicago in the United States ($n = 20$), and the Mayo Clinic in the United States ($n = 17$) published the most papers. Regarding authors, Rutgeerts P in Belgium ($n = 32$), Sandborn WJ in the United States ($n = 23$), and Feagan BG in

Country/Territory of origin: China**Specialty type:** Gastroenterology and hepatology**Provenance and peer review:**

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Canada ($n = 18$) published the highest number of studies. The cooperation relationships between the United States and Europe were most frequent. *Gastroenterology* (impact factor = 22.682) published the most articles on biologic therapy for CD ($n = 32$) with 17654 total citations. Anti-tumor necrosis factor biologics and monoclonal antibodies were the most studied topics.

CONCLUSION

The bibliometric analysis emphasized the key contributions to the development of the specialized field. These data would provide useful research insights into biologic therapy for CD for clinicians and researchers.

Key Words: Biologic therapy; Crohn's disease; Bibliometric analysis; Most influential; Insight

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Core Tip: We conducted a bibliometric analysis from the top 100 highest-cited original articles to determine knowledge gaps and identify areas of interest of biologic therapy for Crohn's disease (CD). The 2000s yielded the most influential original articles and saw the most dramatic growth. The United States and Europe contributed the most publications, and the cooperation relationships between them were most frequent. *Gastroenterology* published the most articles on biologic therapy for CD. Anti-tumor necrosis factor (TNF) biologics and monoclonal antibodies were the most studied topics. These data would provide useful research insights into biologic therapy for CD for clinicians and researchers.

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INTRODUCTION

Crohn's disease (CD), the main type of inflammatory bowel disease, is characterized as chronic, refractory, and relapsing transmural inflammation of the digestive tract[1]. Due to the continuous activation of the intestinal immune system, CD patients would suffer chronic abdominal pain, diarrhea, weight loss, malnutrition, and other obstructive symptoms[2]. Previously, the therapeutic strategy for CD was limited to corticosteroids[3], immunomodulators [methotrexate and thiopurines (azathioprine and mercaptopurine)][4-6], and surgery[7,8]. In the past 3 decades, multiple biologics emerged for CD management, including anti-tumor necrosis factor (TNF) agents (infliximab, adalimumab, and certolizumab), anti-integrin agents (vedolizumab and natalizumab), and anti-(IL)-12/23 agent (ustekinumab)[9]. However, it is difficult for researchers to gain critical articles to guide their studies owing to the publication overload of varied scientific quality.

Bibliometrics is an increasingly conducted method for analyzing and summarizing the main characteristics of publications, including the citation count, the cooperative relationships among countries, institutions, and authors, the distribution of journals, and the hotspots in a certain field. By performing bibliometric analysis and creating infographics, researchers can identify and capture the research hotspots and rising patterns. Bibliometric analysis has been broadly performed in various diseases of gastroenterology, such as *Helicobacter pylori* infection[10], irritable bowel syndrome [11], acute pancreatitis[12], inflammatory bowel disease[13], and so on. Although Connelly *et al*[14] conducted a bibliometric analysis of the 100 classic articles in ulcerative colitis and offered a reference of highly-citable manuscripts, no bibliometric analysis of biologic therapy for CD has been reported.

In this study, we aimed to analyze the top 100 highest-cited original articles in the field of biologic therapy for CD over the last 3 decades *via* bibliometric citation

analysis based on the total citations (TC), which reflect the direct academic significance of a study. In turn, the analysis would provide clinicians and researchers the meaningful insights into the future directions related to biologic therapy for CD.

MATERIALS AND METHODS

Literature search and screening

A systematic search of literature from January 1991 to December 2020 was performed in the Clarivate Analytics Web of Science Core Collection (WOSCC) database. We used search terms including “biologic therapy,” “Crohn disease,” “anti-tumor necrosis factor,” “infliximab,” “adalimumab,” “certolizumab,” “anti-integrin,” “vedolizumab,” “natalizumab,” “anti-IL-12/23,” “ustekinumab,” and their synonyms. The search strategy was shown in [Supplementary Table 1](#). Original articles whose main topic was biologic therapy for CD were included. Literature that was not related to biologic therapy for CD was excluded, and reviews, commentary, case reports, editorials, consensus statements, and guidelines were also excluded. Two reviewers (J.L.S. and Z.Z.) independently identified the top 100 highest-cited original articles based on TC, and a third reviewer (J.S.C.) was recruited for discussion until any disagreement was settled.

Statistical analysis

After identifying the top 100 highest-cited original articles, the records with all available information were downloaded from the WOSCC database. Then, the bibliographic information of the top 100 highest-cited studies was converted and analyzed automatically by R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria) with the “bibliometric” package[15]. We further extracted and analyzed the information, including title, author, institution, country, TC, publication year, journal, 2020 Journal Citation Reports impact factor (IF), and keywords, using the “bibliometric” package.

All collected data were entered in a spreadsheet and manipulated using Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, United States). Graphs and figures were created by using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Microsoft Excel 2019 Power Map (Microsoft Corp., Redmond, WA, United States) was utilized for a global map of countries’ publications of the top 100 highest-cited original articles. We used the VOS viewer (Version 1.6.10) to produce author cooperation network map, institution cooperation network map, keyword clustering map, and so on. The cooperation network map among all countries and the tree map of keywords were created on an online platform of bibliometric analysis (<https://bibliometric.com/>). Finally, 2 researchers (Z.Z. and J.S.C) verified the collected data and further analysis independently.

RESULTS

Publication and citation count

A total of 5489 original articles focusing on biologic therapy for CD were identified from the WOSCC database from January 1991 to December 2020. The top 100 highest-cited original articles were listed in [Supplementary Table 2](#) according to the descending order of TC, and the TC ranged from 2978[16] to 307[17]. The earliest influential original article, which focused on treating CD with anti-TNF and gained TC of 926, was published in 1995[18]. The latest original articles were 4 studies published in 2017 that focused on biologic therapy for CD, including infliximab, adalimumab, and vedolizumab. Both the annual and the cumulative number of publications over the last 3 decades were presented in [Figure 1](#). Interestingly, the 2000s (Period II, $n = 66$) yielded the most influential original articles and saw the most dramatic growth of them, followed by the 2010s (Period III, $n = 28$) and the 1990s (Period I, $n = 6$). Notably, the annual number of publications reached a peak of 11 in the year 2007 in Period II.

Countries

In analyzing the countries to identify the high-impact countries in this field, the top 100 highest-cited original articles originated from 15 countries ([Figure 2](#)). The top 10 countries with the most publications were listed in [Table 1](#), including 8 European countries and 2 North American countries. Among the top 100 highest-cited original

Table 1 Top 10 countries with the most publications

Country	Publication	TC	TC/Publication
United States	37	26179	708
Belgium	20	13325	666
France	9	6791	755
Germany	9	4768	530
Spain	6	2916	486
United Kingdom	5	1980	396
Netherlands	4	2408	602
Norway	2	1163	582
Canada	2	816	408
Switzerland	1	872	872

TC: Total citation.

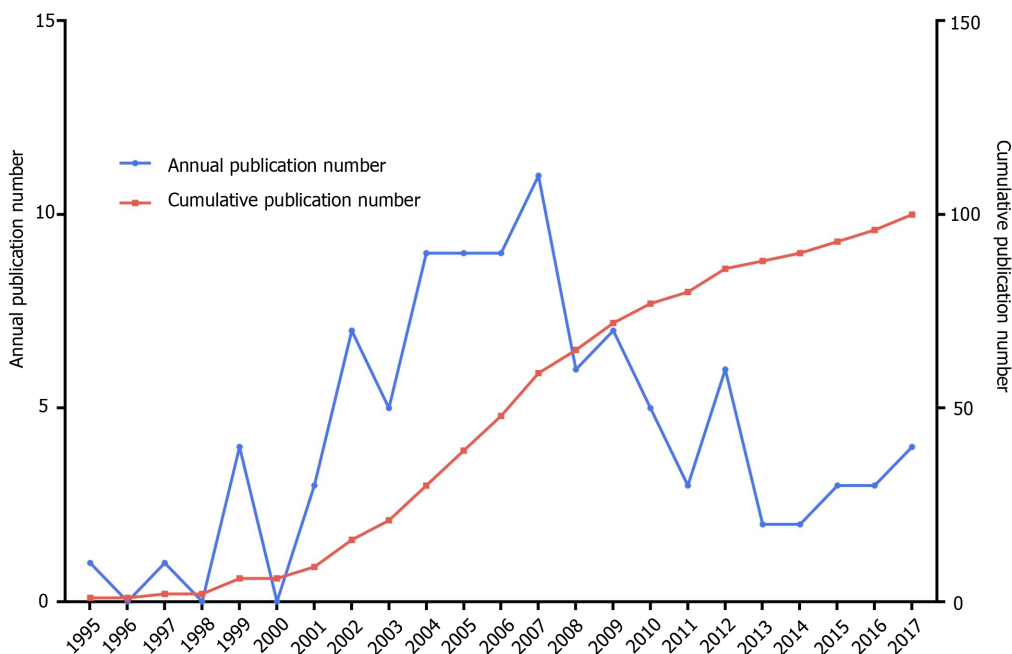


Figure 1 Growth curve of the top 100 highest-cited original articles.

articles, the United States published the most articles ($n = 37$), followed by Belgium ($n = 20$), France ($n = 9$), Germany ($n = 9$), Spain ($n = 6$), United Kingdom ($n = 5$), Netherlands ($n = 4$), Norway ($n = 2$), Canada ($n = 2$), and Switzerland ($n = 1$). Notably, the United States has contributed the most studies and TC in the field of biologic therapy for CD, publishing 37 influential articles and 26179 citations. Meanwhile, as the top high-yield country in Europe, Belgium has published 20 articles with a TC of 13325. The ratio of TC to publication represented the average number of citations of each article, namely the average influence of each study. Although Switzerland ranked tenth in the number of original articles, contributing merely 1 article, it had the highest TC/Publication of 872. To be specific, Hueber *W et al*[19] from Switzerland conducted a randomized, double-blind placebo-controlled trial to explore the effect of a human anti-IL-17A monoclonal antibody, namely secukinumab, for moderate to severe CD, and they failed that blockade of IL-17A was ineffective and caused higher rates of adverse events. Thus, the scientific quality of the research in Switzerland may be generally high. Figure 3 showed the cooperation relationships among countries that contributed to the top 100 highest-cited original articles. The United States, Belgium,

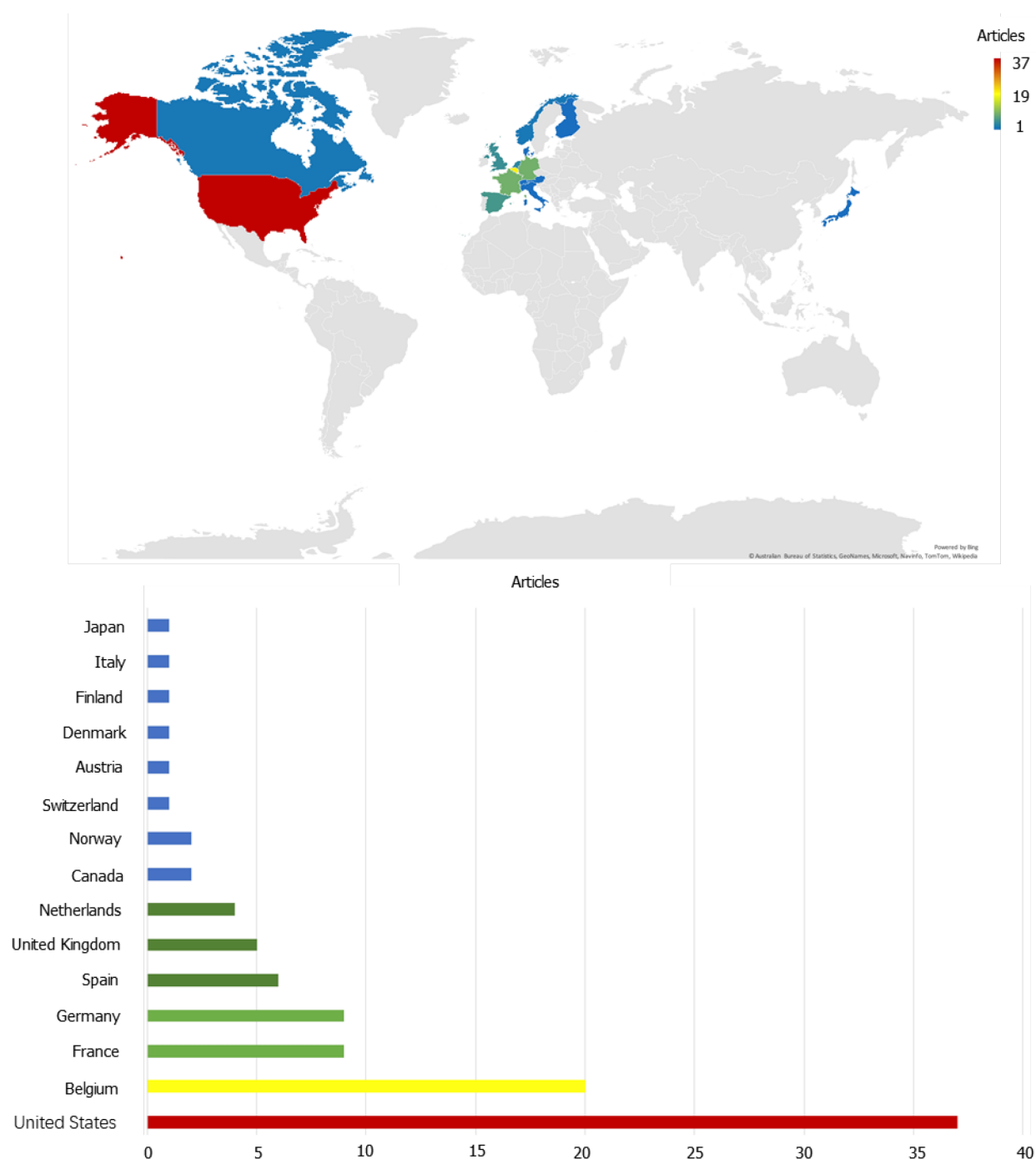


Figure 2 Number of the top 100 highest-cited original articles by country.

France, and Germany were intuitively observed to be involved in the close partnership.

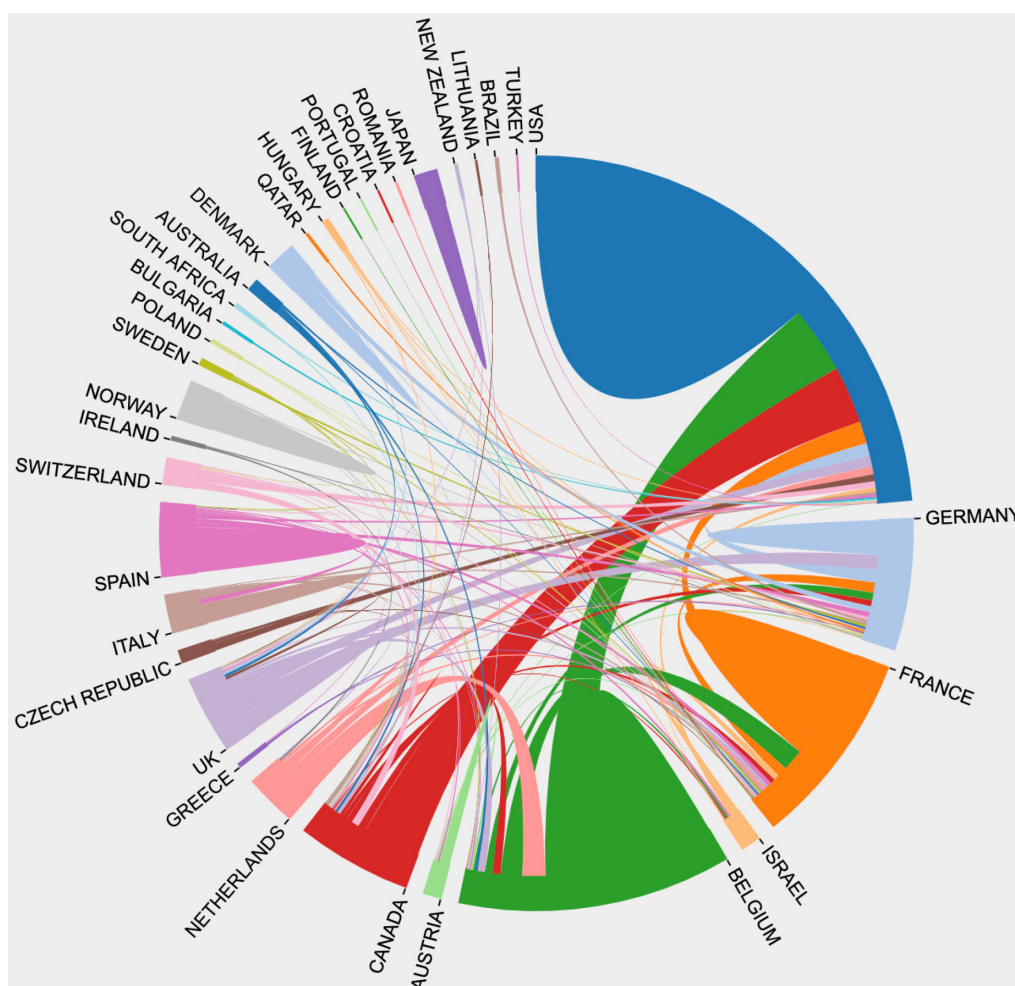
Institutions

The top 10 institutions with the most publications were listed in Table 2, including the University Hospital Gasthuisberg in Belgium, the University of Chicago in the United States, and the Mayo Clinic in the United States with 23, 20, and 17 papers, respectively, and with 17529 citations, 19342 citations, and 14879 citations, respectively. Although the University of Chicago ranked second in the publications, it had the highest TC/Publication of 967, followed by the University of Western Ontario (TC/Publication = 952), the University of Pennsylvania (TC/Publication = 909), and the University Hospital Kiel (TC/Publication = 907). The average citations per article exceeded 900 for these 4 institutions above. The cooperation between institutions was a critical factor in promoting technological development, and Figure 4 showed the cooperation relationships of institutions that have co-published more than three top-

Table 2 Top 10 institutions with the most publications

Institutions	Publication	TC	TC/Publication
University Hosp Gasthuisberg	23	17529	762
University of Chicago	20	19342	967
Mayo Clinic	17	14879	875
University of Western Ontario	15	14284	952
University of Amsterdam	12	9082	757
University of Calgary	11	7255	660
University of Pennsylvania	10	9086	909
University of Kiel	10	9066	907
University of California San Diego	9	4450	494
Abbott Labs	6	4614	769

TC: Total citation.

**Figure 3 Cooperation relationships among all countries.** UK: United Kingdom; USA: United States of America.

cited articles.

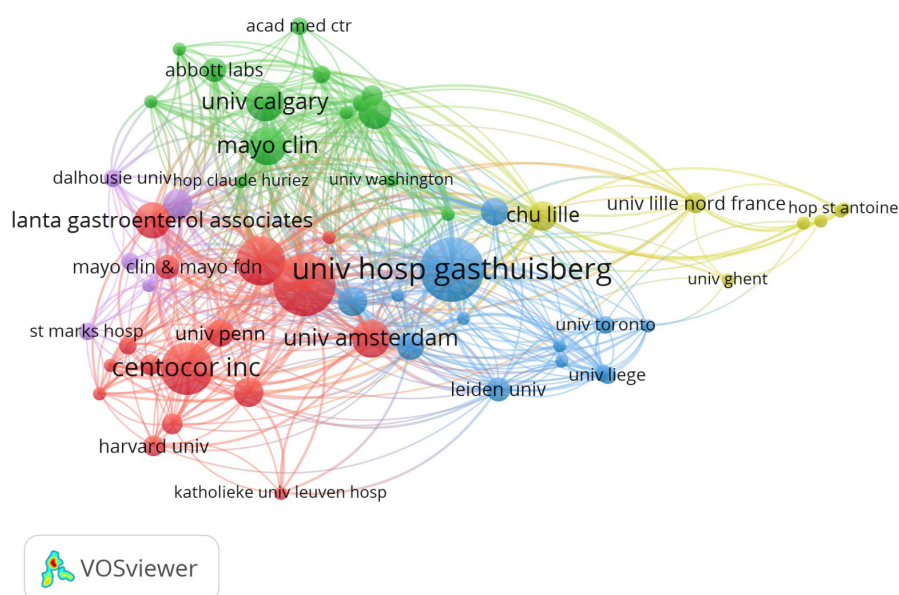
Authors

The top 10 most influential authors with the most publications were listed in Table 3, including Rutgeerts P in Belgium, Sandborn WJ in the United States, and Feagan BG in

Table 3 Top 10 authors with the most publications

Authors	Publication	TC	TC/Publication
Rutgeerts P	32	26039	814
Sandborn WJ	23	18034	784
Feagan BG	18	16127	896
Colombel JF	18	14724	818
Hanauer SB	14	13785	985
D'haens G	13	8951	689
Van Assche G	13	8286	637
Vermeire S	12	6902	575
Sands BE	9	6988	776
Panaccione R	9	5976	664

TC: Total citation.

**Figure 4 Cooperation relationships of institutions that have co-published more than three top-cited articles.**

Canada with 32, 23, and 18 papers, respectively, and with 26039 citations, 18034 citations, and 16127 citations, respectively. Notably, Hanauer SB in the United States had the highest TC/Publication with merely 14 publications, which meant that his studies were of high scientific quality. The partnership among authors that have co-published more than 3 top-cited articles was shown in Figure 5.

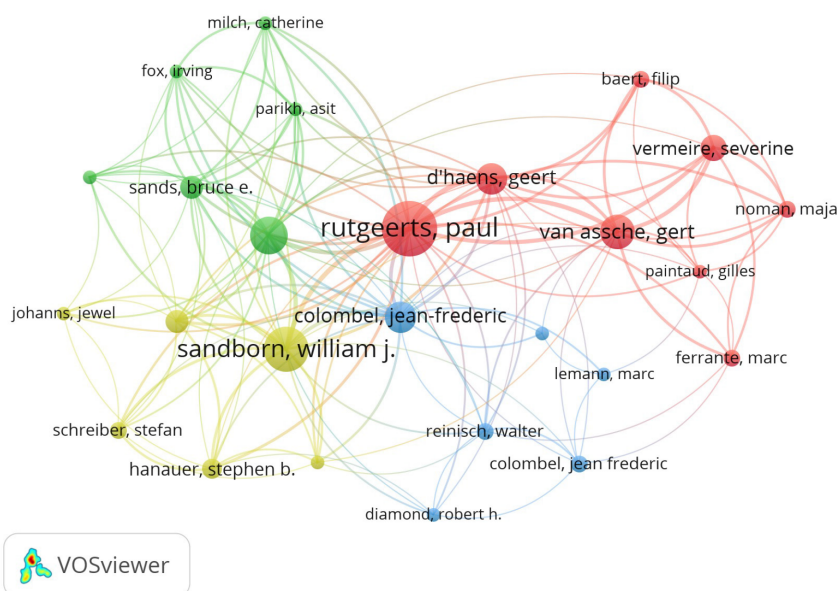
Journals

Based on the descending order of the number of the top 100 most influential original articles, the top 10 journals were listed in Table 4. Over the last 3 decades, *Gastroenterology* (IF = 22.682) has published the extremely most articles on biologic therapy for CD, including 32 publications and 17654 TC. Among the top 10 most influential journals, 5 journals had TC/Publication exceeding 500, in which *The New England Journal of Medicine* had the highest IF of 91.245, the highest TC of 18379, and the highest TC/Publication of 1225, exceeding 90, 18000, and 1225, respectively. The rest were *The Lancet* (IF = 79.321, TC/Publication = 855), *Journal of Crohn's and Colitis* (IF = 9.071, TC/Publication = 799), *Annals of Internal Medicine* (IF = 25.391, TC/Publication = 668), and *Gastroenterology* (IF = 22.682, TC/Publication = 552).

Table 4 Top 10 journals with the most publications

Journal	Publication	2020 IF	TC	TC/Publication
<i>Gastroenterology</i>	32	22.682	17654	552
<i>New England Journal of Medicine</i>	15	91.245	18379	1225
<i>Gut</i>	10	23.059	4693	469
<i>Lancet</i>	7	79.321	5988	855
<i>Clinical Gastroenterology and Hepatology</i>	6	11.382	2860	477
<i>American Journal of Gastroenterology</i>	5	10.864	1854	371
<i>Journal of Crohn's and Colitis</i>	3	9.071	2397	799
<i>Inflammatory Bowel Diseases</i>	3	5.325	1127	376
<i>Arthritis and Rheumatology</i>	2	10.995	810	405
<i>Annals of Internal Medicine</i>	1	25.391	668	668

TC: Total citation; IF: Impact factor.

**Figure 5** Cooperation relationships of authors that have co-published more than three top-cited articles.

Analysis of keywords

The research hotspots in the field of biologic therapy for CD were explored and demonstrated in the treemap (Figure 6). Infliximab, tumor necrosis factor, monoclonal antibody, and adalimumab accounted for 9%, 5%, 3%, and 2% of keywords, respectively. The cluster analysis of keywords that appeared more than seven times was also conducted to validate the results (Figure 7).

DISCUSSION

Due to the lack of a systematic approach to identifying the important information, it is challenging for clinicians and researchers to review the development of biological therapy for CD over the past 3 decades. In the study, we identified and ranked the top 100 highest-cited original articles by TC according to the WOSCC database. Through the bibliometric analysis, we summarized the basic characteristics of these original articles, such as publication, citation, countries, institutions, authors, journals, and keywords. In addition, we could identify research hotspots of biologic therapy for CD.

Tree

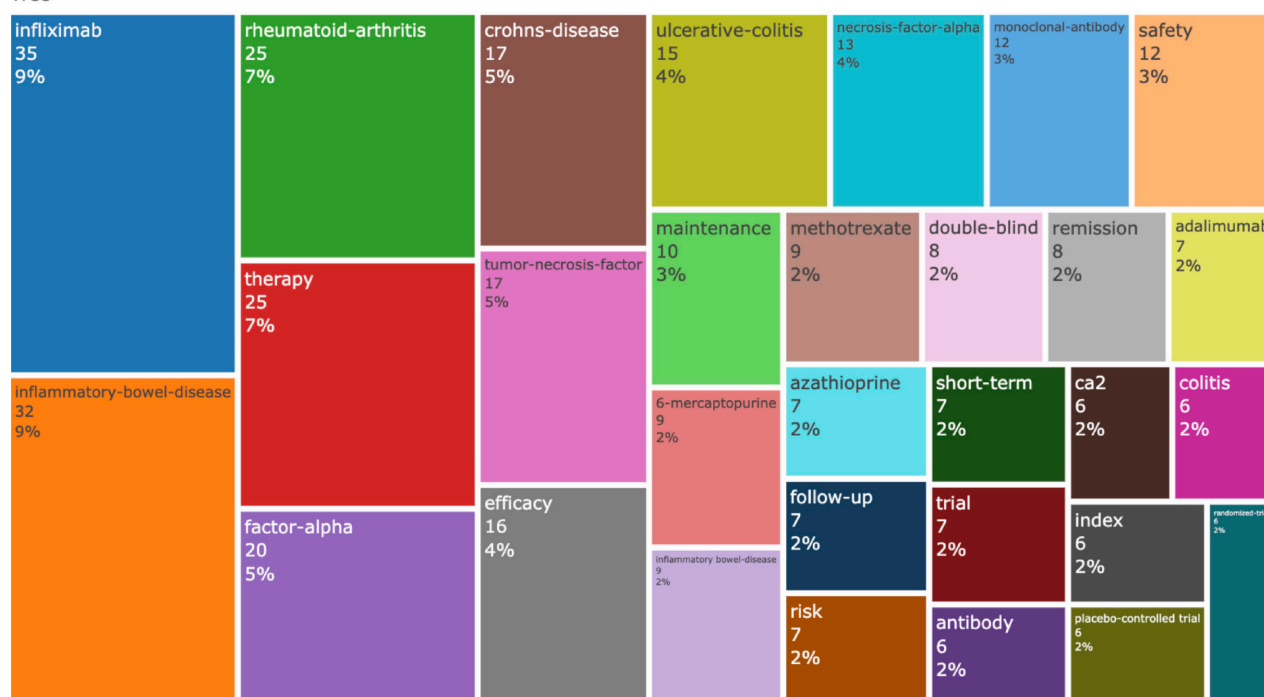


Figure 6 Treemap of keywords of the top 100 highest-cited original articles.

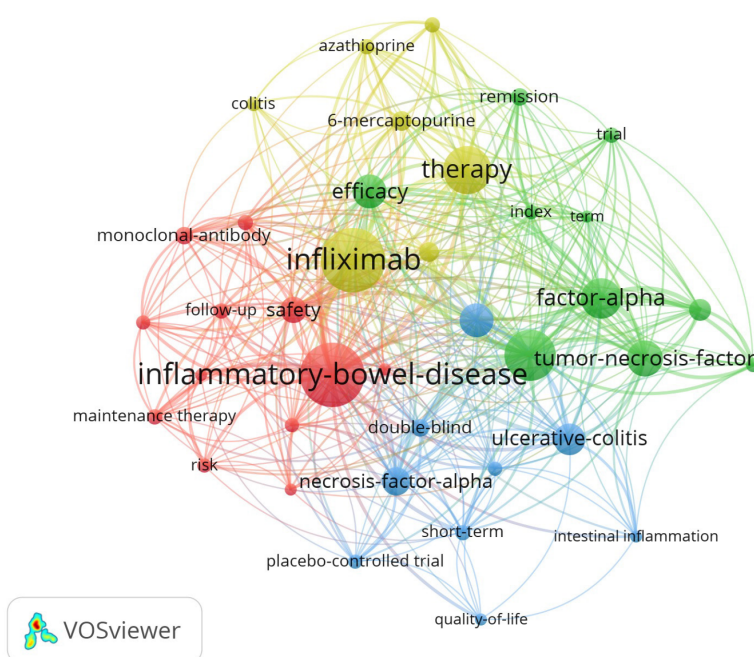


Figure 7 Cluster analysis of keywords that appeared more than seven times.

The analysis of annual and cumulative publications in different publication periods (Period I, Period II, and Period III) enabled clinicians and researchers to understand the development of biologic therapy for CD intuitively. In the 1990s (Period I), the number of most influential articles grew slowly. Notably, there was an explosive growth of the number of studies in the 2000s (Period II) because the first biologic agent, infliximab, was approved for CD treatment by the Food and Drug Administration[20]. Meanwhile, an increasing number of clinical trials were designed and conducted during Period II, including the ACCENT I trial (maintenance infliximab for CD)[16], the CLASSIC I and II trials (maintenance adalimumab for CD)[21,22], the CHARM trial (maintenance adalimumab for clinical response and remission of CD)

[23], and other trials (ustekinumab, natalizumab, and certolizumab treatment for CD) [24–26]. Especially in the year of 2007, with the appearance and clinical use of adalimumab, certolizumab, and natalizumab, the annual publications peaked. However, less high-cited articles were published since the 2010s (Period III). A possible explanation was that the emerging biologics were relatively novel drugs, and the TC of related articles could not be accumulated within the limited time. A study conducted by Azer *et al* [27] further confirmed that the year of publication would be relative to TC, and therefore the TC of recently published articles was low.

The contributions of countries, institutions, and authors to biologic therapy for CD were identified in the study. The top 10 countries with the most publications were 2 North American countries and 8 European countries because the highest incidence rates have been shown in the United States and Europe [28]. This phenomenon may be attributed to the confounding factors of genetics and the environment [29], and the latter, including diet, pollution, microbial exposure, and sanitation, were implicated in the development of CD [30]. Notably, the United States, Belgium, France, and Germany occupied the leading positions and had the most cooperation among them in biologic therapy for CD, thus generating the most high-cited original articles with the highest TC in this field. Rutgeerts P from Belgium and Sandborn WJ from the United States have published the most influential studies and made excellent contributions to biologic therapy for CD, which was worth remembering. More attention should be paid to international cooperation, but it is not limited to the United States and Europe. Further multicenter clinical trials among different countries should be performed to offer evidence for biologic therapy for CD in the future.

Various medical journals were engaged in promoting the development of biologic therapy for CD. In terms of influence, the top 10 journals with the most publications were *Gastroenterology*, *The New England Journal of Medicine*, and *Gut*, with a total of 57 articles. The others were *The Lancet*, *Clinical Gastroenterology and Hepatology*, *American Journal of Gastroenterology*, *Journal of Crohn's and Colitis*, *Inflammatory Bowel Disease*, *Arthritis Rheumatology*, and *Annals of Internal Medicine*, making a total of 27 publications. The top 10 journals were mostly in the field of digestive diseases, while some of them were comprehensive journals, namely *The New England Journal of Medicine* and *The Lancet*. Both journals have relatively high IF of 91.245 and 79.321, respectively, with high TC/Publication of 1225 and 855, respectively. The high scientific level of clinical trials in the top-cited original articles could contribute a lot to the higher citations per paper. One of the significant clinical trials, which was called the ACCENT I randomized trial, was focused on maintenance infliximab for CD and published in *The Lancet* with the highest TC of 2978 [16].

The research hotspots in the top 100 highest-cited original articles over the past 3 decades were infliximab, tumor necrosis factor, monoclonal antibody, and adalimumab treatment for CD, which belonged to the anti-TNF research. The anti-TNF biologics were approved by Food and Drug Administration in an early stage and have achieved excellent curative effects in clinical use. However, other biologics such as anti-integrin agents (vedolizumab and natalizumab) and anti-IL-12/23 agents (ustekinumab) emerged later, and most of them were still in the clinical trial stage. Thus the related original articles have not gained high TC. However, more influential articles would be published as the studies of novel biologics continue.

The study had several limitations that needed to be discussed. First, the current study may not include all influential articles in the field of biologic therapy for CD merely based on the WOSCC database. Although we did utilize broad search terms to search all related articles, it is possible that the search strategy may have missed some crucial literature. Further bibliometric analysis would be conducted with a precise search strategy from WOSCC, PubMed, and PMC databases. Second, the potential citation biases may affect the list of the top 100 highest-cited original articles and subsequently generate inaccurate results. In particular, the latest articles may have insufficient time to accumulate TC. Inappropriate citations, including self-citations, institutional biases, powerful author biases, and language biases, may also be inevitable and further affect the results of the analysis potentially.

CONCLUSION

In summary, the top 100 highest-cited original articles of biologic therapy for CD over the last 3 decades were identified and entered a bibliometric analysis to provide useful insights for clinicians and researchers. Moreover, the study offered an overview of countries, institutions, authors, and journals that had contributed significantly to the

development of the specialized field. We focused on study keywords to explore the current and future research hotspots of biologic therapy for CD. Undoubtedly, studies and innovation of the field will continue to evolve and become an area of interest in the future.

ARTICLE HIGHLIGHTS

Research background

There is an overloading amount of publications on biologic therapy for Crohn's disease (CD).

Research motivation

No comprehensive analysis of biologic therapy for CD has been reported.

Research objectives

To determine knowledge gaps and identify areas of interest of biologic therapy for CD.

Research methods

We conducted a bibliometric analysis of biologic therapy for CD based on the top 100 highest-cited original articles, summarized the bibliographic information, and explored the research hotspots.

Research results

The 2000s yielded the most influential original articles and saw the most dramatic growth. The United States and Europe contributed the most publications, and the cooperation relationships between them were most frequent. *Gastroenterology* published the most articles on biologic therapy for CD. Anti-tumor necrosis factor biologics and monoclonal antibodies were the most studied topics.

Research conclusions

The bibliometric analysis emphasized the key contributions made to the development of the specialized field.

Research perspectives

These data would provide useful research insights into biologic therapy for CD for clinicians and researchers.

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