Top-100 highest-cited original articles in inflammatory bowel disease

A bibliometric analysis

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Abstract

Objectives: The use of citation analysis to identify the first 100 papers in inflammatory bowel disease (IBD) provides unique insights into advances in disease understanding and subsequent follow-up treatment innovations over time.

Methods: The Thomson Reuters Web of Science database with the search terms “inflammatory bowel disease” or “Crohn disease” or “ulcerative colitis” or “colitis” was used to identify all English language full manuscripts for the study. Title, first and senior authors, institution and department of first author, journal, country of origin, year, and topic of each manuscript were analyzed.

Results: The top 100 manuscripts were published between 1955 and 2013. 224,809 eligible papers were returned and the median (range) citation number was 1028.5 (719–3957). The country and year with the greatest number of publications were the USA (n = 47), and 2007 (n = 11). Gastroenterology published the highest number of papers (n = 18, 21,083 citations) and The New England Journal of Medicine had the most citations (n = 13, 25,035 citations).

Conclusions: This highly cited list of papers identifies the subjects and authors who have had the greatest impact on IBD research in the last decades, which serves as a reference for researchers and clinicians “highly citable” manuscripts.

Abbreviations: IBD = inflammatory bowel disease, CD = Crohn disease, UC = ulcerative colitis, ISI = Institute for Scientific Information.

Keywords: bibliometric analysis, Crohn disease, inflammatory bowel disease, ulcerative colitis

Key issues

• Over 242,272 manuscripts on IBD have been published to date.

• These manuscripts have shaped the current understanding of the etiology of IBD, which is an interplay between host environmental factors in a genetically predisposed host.

• Bibliometric citation analysis studies the clinical and scientific significance of manuscripts by analyzing the number of times a work has been cited in subsequent manuscripts. This type of analysis has never before been performed for inflammatory bowel disease.

• The journals publishing the top 100 cited IBD manuscripts are basic science, clinical, epidemiological, surgical, and genetic in nature.

• Rutgeerts P from the Katholieke Univ Leuven Hosp, Louvain, Belgium had the highest amount of authorships (3 first and 3 senior) and citations (n = 6714) followed by Colombel JF of the CHU Lille, Hop Claude Huriez, Dept Hepatogastroenterol, Rue Michel Polonovsky, F-59037 Lille, France (Two first and 3 senior authorships, 6212 citations).

• The year that yielded the highest number of papers was 2007 (n = 11 manuscripts and 16,343 citations) followed by 2000, 2006, and 2008, each with 6 publications (Fig. 1) and 5928, 6750, and 6914 citations (Fig. 2), respectively.

• The institutions with the highest number of publications in the top 100 were NIAID Mucosal Immun Sect and Yale University USA, each with 5 papers generating 5694 and 8216 citations, respectively.
1. Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory condition primarily involving the gastrointestinal tract. It includes Crohn disease (CD), ulcerative colitis (UC), and a less common phenotype-IBD unclassified. It is thought to result from a complex interplay of environmental, microbial, and host factors including genetic factors, although the exact mechanism is not known. CD is a chronic bowel disease characterized by a relapsing inflammatory process. It can affect any part of the gastrointestinal tract and is associated with discontinuous, transmural lesions of the gut wall. UC is a typically relapsing, remitting inflammatory disease of the colon and rectum. The mucosal inflammation is continuous and most commonly progresses proximally from the rectum. Although IBD is mostly seen in Western world, recent data suggests that the incidence and prevalence are increasing worldwide. It can affect people of all ages, including children and geriatric populations, and can affect all aspects of life. The most accepted hypothesis of IBD pathogenesis is that complex interactions between genetics, environmental factors, and the host immune system lead to aberrant immune responses and chronic intestinal inflammation. Currently, the treatment of IBD mainly includes drugs, surgery, and nutritional support. Among them, the commonly used therapeutic drugs, such as aminosalicylic acid, hormones, immunosuppressive agents, etc., have more limited therapeutic effects and more side effects. With a lot of in-depth research, more treatments have been proposed. Such as biosimilar medicines, probiotics, fecal transplantation, diet therapy, and so on.

Bibliometric citation analysis studies the clinical and scientific significance of manuscripts by analyzing the number of citations in subsequent manuscripts. A higher number of citations can represent the contribution of the manuscript to the current subject knowledge system. Bibliometric citations analysis has been utilized to report the top 100 cited papers in medicine and surgery including the subspecialties of orthopedic surgery, ophthalmology, gastric cancer, osteosarcoma, and pituitary adenoma. To date, no study has been undertaken to determine the most influential papers in the field of inflammatory bowel disease. We aim to analyze the most cited papers in IBD to provide insights into how the understanding of disease pathophysiology and treatment over the past 100 years has evolved and to highlight the key work of clinicians and scientists.

2. Materials and methods

To identify the 100 most-cited articles in inflammatory bowel disease, we used Institute for Scientific Information (ISI) Web of Knowledge Journal Citation Reports Science Edition 2015 (Thomson Reuters, New York, NY). Since there was no use of human subjects, our study was exempt from the institutional review board approval. Two authors (XC and YX) extracted the data using a predetermined form. After extraction, data were compared by XC, with disagreements being solved by consensus. We included articles pertaining to inflammatory bowel disease limited to chronic relapsing inflammatory disorders Crohn disease and ulcerative colitis. The keywords used for the search were “inflammatory bowel disease” or “Crohn disease” or “ulcerative colitis” or “colitis” as the “topic” (title, abstract, author’s keywords, and KeyWords Plus). The returned dataset was filtered to include only English language and full manuscripts and sorted by number of citations.

![Figure 1. Number of top 100 of publications per year.](image-url)
a method initially developed by Paladugu et al. Time limitations were not implemented in the investigation, and we did not impose any restrictions on the type of research, the availability of abstracts, and human and nonhuman research subjects. The results were organized from the most cited to the least cited publications. If we found identical numbers of total citations, the more recent articles were ranked higher. Data retrieved included journal name, publication date, first and senior authors, year of publication, country of origin, total number of citations for the article, overall citation rate (total citations/article age), current citation rate (measured as the number of citations in the year 2017), and research nature (basic science, clinical research or review).

3. Results

The Web of Knowledge search returned 242,272 works, of which 224,809 were in the English language. The top 100 cited manuscripts are listed in Table 1. The citation count of articles ranged from 719 to 4957 (median number of citations, 1028.5). Citations Per Year The citations per year ranged from 18.29 to 400.33 (median, 70.49). The rank according to the average number of citations per year is shown in Table 1. The earliest and most cited manuscript was published in 1955 and focused on cortisone, the first treatment for UC. The most recent was published in 2013 and focused on new insight into the mechanisms by which host–microbe interactions establish immunological homeostasis in the gut.
The 100 most-cited articles in inflammatory bowel disease.

| Rank | Article                                                                 | Citations | Citations/year since publication | Rank according to average citations per year | Citations in 2018 | Year       |
|------|-------------------------------------------------------------------------|-----------|---------------------------------|---------------------------------------------|-------------------|------------|
| 1    | Genome-wide association study of 14,000 cases of seven common diseases and 3000 shared controls [16] | 4967      | 413.08                          | 1                                           | 176               | 2007       |
| 2    | Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn’s disease [17] | 3609      | 200.5                           | 15                                          | 71                | 2001       |
| 3    | A frameshift mutation in NOD2 associated with susceptibility to Crohn’s disease [18] | 3329      | 184.94                          | 21                                          | 66                | 2001       |
| 4    | Interleukin-10-deficient mice develop chronic enterocolitis [19]          | 3017      | 116.04                          | 2                                           | 54                | 1993       |
| 5    | A CD4 (+) T-cell subset inhibits antigen-specific T-cell responses and prevents colitis [20] | 2758      | 125.82                          | 3                                           | 35                | 1997       |
| 6    | Development of a Crohn-disease activity index - national cooperative Crohn’s-disease study [21] | 2579      | 59.98                           | 10                                          | 57                | 1976       |
| 7    | Maintenance infliximab for Crohn’s disease: the ACCENT I randomised trial [22] | 2524      | 148.47                          | 52                                          | 114               | 2002       |
| 8    | Inflammatory bowel disease [23]                                          | 2453      | 144.29                          | 29                                          | 46                | 2002       |
| 9    | A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn’s disease [24] | 2392      | 108.73                          | 30                                          | 35                | 1997       |
| 10   | Unravelling the pathogenesis of inflammatory bowel disease [25]          | 2106      | 175.5                           | 17                                          | 107               | 2007       |
| 11   | Infliximab for induction and maintenance therapy for ulcerative colitis [26] | 1911      | 136.5                           | 7                                           | 106               | 2005       |
| 12   | Cortisone in ulcerative colitis - final report on a therapeutic trial [27] | 1899      | 29.67                           | 16                                          | 30                | 1987       |
| 13   | A genome-wide association study identifies IL23R as an inflammatory bowel disease gene [28] | 1892      | 145.54                          | 13                                          | 50                | 2006       |
| 14   | Infliximab for the treatment of fistulas in patients with Crohn’s disease [29] | 1757      | 87.85                           | 8                                           | 30                | 1999       |
| 15   | Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease [30] | 1752      | 250.29                          | 11                                          | 185               | 2012       |
| 16   | Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases [31] | 1752      | 146.24                          | 23                                          | 136               | 2007       |
| 17   | Genome-wide association defines more than 30 distinct susceptibility loci for Crohn’s disease [32] | 1669      | 151.73                          | 5                                           | 63                | 2008       |
| 18   | Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influence [33] | 1619      | 107.93                          | 41                                          | 70                | 2004       |
| 19   | IKK beta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer [34] | 1587      | 105.8                           | 4                                           | 54                | 2004       |
| 20   | Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25 (+) CD4 (+) regulatory cells that control intestinal inflammation [35] | 1570      | 82.63                           | 73                                          | 19                | 2000       |
| 21   | Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review [36] | 1568      | 224.8                          | 9                                           | 201               | 2012       |
| 22   | Inflammatory bowel disease: etiology and pathogenesis [27] | 1562      | 74.38                           | 18                                          | 24                | 1998       |
| 23   | Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients [37] | 1462      | 132.91                          | 19                                          | 128               | 2008       |
| 24   | Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection [38] | 1458      | 91.13                           | 49                                          | 41                | 2003       |
| 25   | Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology [39] | 1443      | 103.07                          | 85                                          | 98                | 2005       |
| 26   | The risk of colorectal cancer in ulcerative colitis: a meta-analysis [40] | 1436      | 79.78                           | 50                                          | 63                | 2001       |
| 27   | A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice [41] | 1427      | 49.21                           | 25                                          | 47                | 1990       |
| 28   | Dysplasia in inflammatory bowel-disease - standardized classification with provisional clinical-applications [42] | 1410      | 39.17                           | 68                                          | 13                | 1983       |
| 29   | Infliximab, azathioprine, or combination therapy for Crohn’s disease [43] | 1385      | 153.89                          | 38                                          | 130               | 2010       |
| 30   | Genome-wide meta-analysis increases to 71 the number of confirmed Crohn’s disease susceptibility loci [44] | 1378      | 153.11                          | 70                                          | 85                | 2010       |
| 31   | Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene [45] | 1373      | 52.81                           | 39                                          | 15                | 1993       |
| 32   | Influence of immunogenicity on the long-term efficacy of infliximab in Crohn’s disease [47] | 1326      | 82.88                           | 43                                          | 44                | 2003       |
| 33   | Hapten-induced model of chronic inflammation and ulceration in the rat colon [48] | 1261      | 42.03                           | 51                                          | 25                | 1989       |
| 34   | Clinicopathological study of dextran sulfate sodium experimental murine colitis [49] | 1257      | 48.35                           | 54                                          | 57                | 1993       |
| 35   | Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative-colitis - a randomized study [50] | 1215      | 37.97                           | 24                                          | 90                | 1987       |
| 36   | Ulcerative-colitis and colorectal-cancer - a population-based study [51] | 1187      | 40.93                           | 88                                          | 24                | 1990       |
| 37   | Infliximab maintenance therapy for fistulating Crohn’s disease [52] | 1186      | 79.07                           | 14                                          | 52                | 2004       |
| 38   | Adalimumab for maintenance of clinical response and remission in patients with Crohn disease: The CHARM trial [53] | 1181      | 98.42                           | 59                                          | 86                | 2007       |
| 39   | Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis [54] | 1174      | 97.83                           | 47                                          | 31                | 2007       |
| 40   | Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract [55] | 1165      | 83.21                           | 40                                          | 29                | 2005       |
| 41   | Mechanisms of disease inflammatory bowel disease [56] | 1164      | 116.4                           | 32                                          | 98                | 2009       |
| 42   | Host recognition of bacterial muramyl dipeptide mediated through NOD2 [57] | 1157      | 72.31                           | 20                                          | 25                | 2003       |

(continued)
IL-23 is essential for T cell-mediated colitis and promotes inflammation.

Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1 beta production [69].

Antibodies to interleukin-12 abrogate established experimental colitis in mice [68].

Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells [67].

A microbial symbiosis factor prevents intestinal inflammation.

IL-6 and Stat3 Are Required for Survival of Intestinal Epithelial Cells and Development of Colitis-Associated Cancer [63].

The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications [62].

National Cooperative Crohn Disease Study - Results Of Drug-Treatment [63].

The immunological and genetic basis of inflammatory bowel disease.

Cyclosporine in severe ulcerative-colitis refractory to steroid-therapy [60].

The immunological and genetic basis of inflammatory bowel disease.

Human ant-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn disease: the CLASSIC-I trial [78].

Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice [79].

Predictability of the postoperative course of Crohn’s disease [80].

Disparate CD4(+) lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease - Crohn’s disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5 [81].

Gastroenterology 2 - Inflammatory bowel disease: clinical aspects and established and evolving therapies [82].

Inflammatory Bowel Disease [83].

Mucosal flora in inflammatory bowel disease [84].

The second European evidence-based Consensus on the diagnosis and management of Crohn’s disease: Current management [85].

Treatment of Crohn’s disease with 6-mercaptopurine - a long-term, randomized, double-blind-study [86].

Treatment of Crohn’s disease with anti-tumor necrosis factor chimeric monoclonal antibody (CA2) [87].

Gastroenterology 1 - Inflammatory bowel disease: cause and immunobiology [88].
Table 1
(continued).

| Rank | Article                                                                 | Citations/year since publication | Rank according to average citations per year | Citations in 2018 Year |
|------|--------------------------------------------------------------------------|----------------------------------|---------------------------------------------|------------------------|
| 82   | Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: Evidence in Crohn disease and experimental colitis in vivo[97] | 838                             | 44.11                                       | 28                     | 2000                   |
| 83   | Enhanced Th1 activity and development of chronic enterocolitis in mice devoid of Stat3 in macrophages and neutrophils[50] | 834                             | 41.7                                        | 35                     | 16                     | 1999                   |
| 84   | Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease[104] | 833                             | 41.65                                       | 98                     | 16                     | 1999                   |
| 85   | NLRP6 Inflammasome Regulates Colonic Microbial Ecology and Risk for Colitis[100] | 832                             | 104                                         | 72                     | 75                     | 2011                   |
| 86   | Classification of inflammatory bowel-disease[103]                        | 824                             | 27.47                                       | 79                     | 34                     | 1989                   |
| 87   | European cooperative Crohn’s-disease study (ECCDS) - results of drug-treatment[102] | 803                             | 22.94                                       | 92                     | 6                      | 1984                   |
| 88   | Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota[103] | 794                             | 88.22                                       | 96                     | 80                     | 2010                   |
| 89   | A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells[50] | 793                             | 72.09                                       | 65                     | 41                     | 2008                   |
| 90   | Phenotypically distinct subsets of CD4(+) T-cells induce or protect from chronic intestinal inflammation in C - B-17 SCID mice[103] | 793                             | 30.5                                        | 74                     | 17                     | 1993                   |
| 91   | Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative-colitis - a randomized trial[103] | 788                             | 26.27                                       | 90                     | 18                     | 1989                   |
| 92   | Enterocolitis and colon cancer in interleukin-10-deficient mice are associated with aberrant cytokine production and CD4(+) TH1-like responses[107] | 776                             | 33.74                                       | 100                    | 13                     | 1996                   |
| 93   | Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn’s disease susceptibility[106] | 775                             | 64.58                                       | 12                     | 17                     | 2007                   |
| 94   | Proctocolectomy without ileostomy for ulcerative-colitis[106]            | 763                             | 18.61                                       | 86                     | 22                     | 1978                   |
| 95   | Chemically induced mouse models of intestinal inflammation[110]         | 756                             | 63                                          | 48                     | 52                     | 2007                   |
| 96   | Mapping of a susceptibility locus for Crohn’s disease on chromosome 16[111] | 750                             | 32.61                                       | 91                     | 8                      | 1996                   |
| 97   | The fundamental basis of inflammatory bowel disease[112]                | 746                             | 62.17                                       | 87                     | 26                     | 2007                   |
| 98   | Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial[113] | 731                             | 36.55                                       | 71                     | 9                      | 1999                   |
| 99   | The natural history of corticosteroid therapy for inflammatory bowel disease: A population-based study[114] | 721                             | 40.06                                       | 60                     | 18                     | 2001                   |
| 100  | Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD)[115] | 719                             | 29.96                                       | 94                     | 7                      | 1995                   |

Table 2
Journals publishing the top 100 cited IBD manuscripts.

| Journal                                      | Impact factor (IF) | IF without journal self-citations | 5-y IF | Number of manuscripts in the top 100 | Total citations | First issue |
|----------------------------------------------|--------------------|-----------------------------------|--------|--------------------------------------|-----------------|-------------|
| GASTROENTEROLOGY                            | 20.773             | 20.006                            | 19.131 | 18                                   | 21,083          | 1976        |
| NATURE                                       | 41.577             | 41.015                            | 44.958 | 13                                   | 25,035          | 1906        |
| NEW ENGLAND JOURNAL OF MEDICINE             | 79.258             | 78.537                            | 67.512 | 13                                   | 18,844          | 1980        |
| LANCET                                       | 53.254             | 51.806                            | 52.665 | 5                                    | 5850            | 1999        |
| NATURE GENETICS                             | 27.125             | 26.191                            | 31.154 | 5                                    | 6149            | 2007        |
| CELL                                         | 31.598             | 30.790                            | 33.796 | 4                                    | 6809            | 1993        |
| GUT                                          | 17.016             | 16.469                            | 15.910 | 4                                    | 4463            | 2001        |
| JOURNAL OF CLINICAL INVESTIGATION           | 13.251             | 13.093                            | 14.434 | 3                                    | 2520            | 1996        |
| JOURNAL OF EXPERIMENTAL MEDICINE            | 10.709             | 10.514                            | 11.929 | 3                                    | 3691            | 1995        |
| PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA | 9.504             | 9.230                            | 10.359 | 3                                    | 4008            | 2007        |
| SCIENCE                                      | 41.058             | 40.616                            | 40.627 | 3                                    | 3919            | 2002        |
| ANNUAL REVIEW OF IMMUNOLOGY                 | 22.714             | 22.551                            | 35.512 | 2                                    | 1832            | 2002        |
| BRITISH MEDICAL JOURNAL                     |                    |                                   |        |                                      | 2               | 2662        |
| IMMUNITY                                     | 19.734             | 19.100                            | 23.616 | 2                                    | 1687            | 1996        |
| INFECTION AND IMMUNITY                       | 3.256              | 3.070                             | 3.603  | 2                                    | 1773            | 1980        |
| JOURNAL OF BIOLOGICAL CHEMISTRY             | 4.010              | 3.828                             | 4.253  | 2                                    | 2615            | 1999        |
| BMJ-BRITISH MEDICAL JOURNAL                 | 23.259             | 21.852                            | 20.375 | 1                                    | 788             | 2007        |
The top 100 manuscripts were published in 32 journals (Table 2). These journals are basic science, clinical, epidemiological, surgical, and genetic in nature. Gastroenterology published the highest number of top 100 papers (n = 18 with 21,083 citations combined). This was followed by Nature with 13 manuscripts and 25,035 citations. Impact factors of the 32 journals ranged from 79.258 (New England Journal Of Medicine, 13 manuscripts and 18,844 citations) to 1.622 (Canadian Journal of Gastroenterology and Hepatology, 1 manuscript with 1443 citations).

The number of authors in each article ranged from 1 to 194 (median, 7). Eleven authors had more than 1 first authorship (Table 3). Seven had more than 5 senior authorship. Fifteen had at least 1 first and 1 or more senior authorships. Rutgeerts P from the Katholieke Univ Leuven Hosp, Louvain, Belgium had the highest amount of authorships (3 first and 3 senior) and citations (n = 6714) followed by Colombel JF of the CHU Lille, Hop Claude Huriez, Dept Hepatogastroenterol, Rue Michel Polonovski, F-59037 Lille, France (Two first and 3 senior authorships, 6212 citations).

The year which yielded the highest number of papers was 2007 (n = 11 manuscripts and 16,343 citations) followed by 2000, 2006, and 2008, each with 6 publications (Fig. 1) and 5928, 6750, and 6914 citations (Fig. 2), respectively. The articles were published between 1955 and 2013 and most were published in the 5-year periods 2005 to 2009 (n = 29) and 2000 to 2005 (n = 23). The most prolific authors, as demonstrated by the first authorship of 3 or more of the manuscripts, hailed from 11 institutions. Ten of these institutions are located in the United States and 1 in Germany. The institutions with the highest number of publications in the top 100 were NIAID Mucosal Immun Sect and Yale University USA, each with 5 papers generating 5694 and 8216 citations, respectively (Table 4). Forty-seven percent of the manuscripts

### Table 2 (continued).

| Journal                                      | Impact factor (IF) | IF without journal self-citations | 5-y IF | Number of manuscripts in the top 100 | Total citations | First issue |
|----------------------------------------------|--------------------|-----------------------------------|--------|--------------------------------------|-----------------|-------------|
| CANADIAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY | 1.622              | 1.580                             | 2.121  | 1                                    | 1443            | 1993        |
| CANCER CELL                                  | 22.844             | 22.541                            | 27.072 | 1                                    | 1031            | 2001        |
| CLINICAL AND EXPERIMENTAL IMMUNOLOGY         | 3.542              | 3.446                             | 3.234  | 1                                    | 719             | 1996        |
| HUMAN PATHOLOGY                             | 3.125              | 2.841                             | 2.816  | 1                                    | 1410            | 1995        |
| INFLAMMATORY BOWEL DISEASES                 | 4.347              | 3.996                             | 4.872  | 1                                    | 863             | 2007        |
| INTERNATIONAL IMMUNOLOGY                    | 5.189              | 5.147                             | 3.837  | 1                                    | 793             | 2000        |
| JOURNAL OF CROHNS & COLITIS                 | 6.637              | 6.076                             | 6.992  | 1                                    | 885             | 2010        |
| JOURNAL OF IMMUNOLOGY                       | 4.539              | 4.220                             | 4.900  | 1                                    | 907             | 1976        |
| LABORATORY INVESTIGATION                    | 4.254              | 4.161                             | 4.345  | 1                                    | 1257            | 1996        |
| MEDICINE                                    | 2.028              | 1.691                             | 2.193  | 1                                    | 952             | 1980        |
| NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY | 32.621          | 32.357                            | 33.409 | 1                                    | 838             | 2007        |
| NATURE MEDICINE                             | 12.423             | 12.244                            | 15.269 | 1                                    | 756             | 1993        |
| NATURE REVIEWS IMMUNOLOGY                   | 41.982             | 41.642                            | 46.507 | 1                                    | 1139            | 2001        |
| SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY    | 2.629              | 2.537                             | 2.511  | 1                                    | 824             | 1989        |

### Table 3

| Author's name | Number of first authorships | Number of citations from first authorships | Number of senior authorships | Number of citations from senior authorships |
|---------------|----------------------------|-------------------------------------------|-------------------------------|---------------------------------------------|
| Hanauer SB    | 3                          | 4363                                      | 2                             | 3456                                        |
| Rutgeerts P   | 3                          | 3646                                      | 3                             | 3068                                        |
| Baumgart DC   | 2                          | 1741                                      | 1                             | 898                                         |
| Colombel JF   | 2                          | 2542                                      | 3                             | 3670                                        |
| Hanpe J       | 2                          | 2010                                      | 1                             | 1153                                        |
| Hugot JP      | 2                          | 4365                                      | 1                             | 750                                         |
| Podolsky DK   | 2                          | 3306                                      | 4                             | 6282                                        |
| Poonie F      | 2                          | 1657                                      | 3                             | 3216                                        |
| Present DH    | 2                          | 2620                                      | 1                             | 1757                                        |
| Sartor RB     | 2                          | 1812                                      | 2                             | 1817                                        |
| Strober W     | 2                          | 1763                                      | 3                             | 2828                                        |
| Akira S       | 0                          | 775                                       | 3                             | 2758                                        |
| Cho JH        | 0                          | 763                                       | 2                             | 4808                                        |
| Neurath MF    | 1                          | 1026                                      | 3                             | 2604                                        |
| Loftus EV     | 1                          | 1587                                      | 2                             | 2340                                        |
| Mazmanian SK  | 1                          | 998                                       | 2                             | 1820                                        |
| Parkas M      | 1                          | 775                                       | 2                             | 2153                                        |
| Parks AG      | 1                          | 763                                       | 2                             | 3342                                        |
| Riddell RH    | 1                          | 1443                                      | 2                             | 2290                                        |
| Saadat B      | 1                          | 1373                                      | 2                             | 4390                                        |
of the 100 articles, 51 were basic research, 31 were clinical research, and 18 were review papers (among the category "review papers" consensus papers were included). Considering the number of citations per type of article, a statistically significant difference was not found between the groups of basic research and clinical research (Mann–Whitney test \( P = .699 \); basic research: median = 1008 [range = 719–3609]; clinical research: median = 1122 [range = 721–2579]; Table 5). We subdivided clinical research articles according to topics: diagnostic research \( n = 6, 19.35\% \), epidemiology \( n = 3, 9.68\% \), and medical and surgical treatment \( n = 22, 70.97\% \). Eighteen articles were review articles (mean 1478 [range = 824–4957]; Table 5).

The topics covered in the top 100 are wide-ranging (Table 6). Many topics are the topic with the highest amount of publications \( n = 27\) followed by genetics \( n = 26\) and treatment \( n = 16\). Within the manuscripts that focused on molecules, factor-alpha is the topic of interest of the greatest number of manuscripts \( n = 15\), followed by interferon-gamma \( n = 11\), CD4+ T-cells \( n = 10\), and interleukin-10 \( n = 9\). Within the manuscripts that focused on treatment, 6-mercaptopurine, infliximab, and cyclosporin are the topic of interest of the greatest number of manuscripts \( n = 4\) each, followed by 5-amino salicylic acid \( n = 3\). Eight manuscripts focus on the microbiome and 4 focus on epidemiology. Ulcerative colitis \( n = 45\) and Crohn disease \( n = 43\) are the main topics covered in top 100 manuscripts. Sixteen utilized animal models.

### 4. Discussion

Bibliometric studies allow the reader to gain an insight into the history and development of a particular specialty over time.\(^{116}\) Similarly, the identification of citation classics can promote understanding of academic advances in specific areas and help identify emerging themes and future directions in specific disciplines. These most cited works reflect important themes of the scientific and clinical IBD community. Our analysis has identified the most influential articles on the results of inflammatory bowel disease research in the past few decades. This study highlights the contribution of significant advances in inflammatory bowel disease research and points to current trends in the field.

Similar to various other analyses, our bibliometric also has a peak period from 2000 to 2009, with more than half of the most-cited articles being published during this 10-year period. Only 3 articles published since 2012 made it to the list, likely because several years are needed for an article to gain a sufficient number of citations.

The ranking of articles on the basis of citations was considerably different from the original ranking based on citation counts only. However, the article “Genome-wide association study of 14,000 cases of 7 common diseases and 3000 shared controls” by Burton et al, both with the highest average citations per year and total citations, which was originally ranked at number 1. It was published in 2007 and highlights the importance of genome-wide association (GWA) to the identification of genes involved in common human diseases.

The publication of these top 100 manuscripts has several high impacts, reflecting their quality and interest in the science and...
clinical community. The impact factor of a journal quantifies the average citation of manuscripts published in journals over a specified period of time. Therefore, journals with higher impact factors are considered to be of higher quality and are more likely to contain influential publications. Journals with very high impact factors (79.258–31.398); The New England Journal of Medicine, Lancet, Nature Reviews Immunology, Nature, Nature Medicine, Cell and Science represent 40% of all publications in the top 100. Furthermore, the median impact factor was 12.423 and 15% of publications were in journals with an impact factor of 4.539 or less. A possible explanation for this involves the novelty of the results. Novelty can be classified as related to general science or only to inflammatory bowel disease. The findings that have been established in other cancers can then be reconstructed in inflammatory bowel disease. These manuscripts are unlikely to be published in high-impact journals, but they are likely to be considered influential in the context of this study.

Gastroenterology contributes the most articles to our list (n = 18), followed by Nature and New England Journal of Medicine (both n = 13). All these are specific journals catering to a particular field, and according to the Bradford law, this observation is justified. However, several high-impact articles have been published in general medical journals such as The Lancet and Science. Bradford’s Law means that some core journals in a particular field extract most of the citations, which is largely confirmed in our research. Therefore, for researchers, editors, and readers, the publications of journals in specific areas related to IBD may be more influential than publications in general medical journals.

The top 3 most-cited authors in this study period (Podolsky DK, Rutgeerts P, and Burton PR) contributed 14 articles as first and/or senior author, accruing a total of 18,212 citations. Of these 14 articles, 8 were from American institutions and 3 from Belgium. This highlights how a relatively few authors can substantially contribute to the impact of a journal or a field of research. Twenty-seven were found to have 5 or more publications in the top 100 list. Among them, the author with the most articles is Rutgeerts, P. His name appears in more than one-tenth of all the articles on our list. This is a huge contribution to IBD. Other frequent contributors to this field are Colombel, JF and Hanauer, SB, with 10 and 9 publications, respectively. It can be inferred from this finding that a few eminent dedicated researchers contribute to IBD on a scale not observed in other bibliometrics. These researchers are more likely to receive academic promotions as a result of their notable contributions in the literature.

The geographic location of the authors reflects disease distribution. IBD is primarily a disease of Western societies. Forty-one percent of manuscripts were from Europe and 47% from the United States. Conversely, no manuscripts originating from Africa were found and only 5 manuscripts were from Asia (all from Japan). The 100 most-cited articles in inflammatory bowel disease research were published in 32 journals, and 68 of the articles were published in 5 American journals. The American journal “Gastroenterology,” established in 1943, topped the list with 18 articles.

A peak in cytokine research is seen in the early 1990s, when interleukins were a focus of many studies. Another peak in the cytokine research is seen in the early 2000s, at the time of in vivo animal model of colitis. These manuscripts are unlikely to be published in high-impact journals, but they are likely to be considered influential in the context of this study.

When looking specifically at the topics which received a high amount of coverage in the top 100, the treatment in IBD is reflected by 16% of the top 100 (including 3 of the top 10 papers), focusing on the subject. Baumgart’s 1980 paper confirmed 6-mercaptopurine (6-MP) was an effective and useful agent in the management of Crohn disease of 83 CD patients. It was reported that 6-MP was more effective than placebo in closing fistulas and in permitting discontinuation or reduction of steroid dosage. Later Present’s and Ekbom’s work both replicated infliximab was an efficacious treatment for fistulas in patients with Crohn disease in a randomized, multicenter, double-blind, placebo-controlled trial. This manuscript was followed by Colombel’s research-authenticated patients with moderate-to-severe Crohn disease who were treated with infliximab plus azathioprine or infliximab monotherapy were more likely to have a corticosteroid-free Clinical remission than those receiving azathioprine monotherapy. In addition, notable top 100 notable inclusions include Burton’s 2007 landmark paper on the use of GWA to the identification of genes involved in IBD, which offered new avenues for exploring the pathophysiology of these important disorders.

The topics covered in the genetics manuscripts were varied and included papers on genome-wide association study, metagenomic approach, genetic marine models of colitis, and cytokine associated genes. The 1996 Nature manuscript by Strober et al was the first to search genome-wide of IBD on 2 consecutive and independent panels of families with multiple affected members, using a nonparametric 2-point sibling-pair linkage method, identified a putative CD-susceptibility locus on chromosome 16. This authenticated that inherited factors may contribute in part to variation in individual susceptibility to IBD and provided a basis for the pathogenic mechanism of IBD. Number 61 on the list, Furusawa’s 2006 paper on the first use of a comprehensive metagenomic approach to investigate the full range of intestinal microbial diversity, allowed us to detect a reduced complexity of the bacterial phylum Firmicutes as a signature of the faecal microbiota in patients with CD. In addition, bowel inflammation in the mutants which originates from uncontrolled immune responses was stimulated by enteric antigens and IL-10 was an essential immunoregulator in the intestinal tract.

Other works of note include Rutgeerts’ paper that summarized the results of the ACCENT I and II trials proving the efficacy of infliximab, an antitumor necrosis factor agent (which was at the time being used to treat Crohn) in UC, revolutionizing treatment. Okayasu’s 1990 paper on the use of dextran sulfate sodium containing drinking water to induce a UC-like colitis in mice, which is the most commonly utilized nongenetic animal model of colitis, is found at number 6 in the list. Oral administration of a new probiotic preparation (VSL#3) is effective in preventing flare-ups of chronic pouchitis.

The main limitation of this manuscript is that there may be several types of biases that may affect the outcome. Disproportionate references may be due to institutional bias, language bias,
self-citation, or powerful person bias. In addition, older journals may receive more citations. Although trying to control this by using the Citation Index, it may take several years for an influential manuscript to generate a citation due to the time it takes to cite the manuscript. Therefore, the recently published manuscripts have been sufficiently cited to be included in the top 100, which has increased the importance. Another limitation is the institution that includes only the first author and the senior author, as well as the first author. It is possible that several first authors will coauthor other papers in the top 100 and therefore are not represented in the current research report.

5. Conclusion
In conclusion, this is, to our knowledge, the first bibliometric study to identify the 100 most cited papers in inflammatory bowel disease research. The most cited citations emphasized by IBD in the current work can be considered classic works in the field of research, as they have a great influence on subsequent works, which can be proved by their citations. These manuscripts describe the epidemiological, genetic, immunologic, pharmacologic, and surgically relevant disease features. The majority of these works were published in high impact journals reflecting the importance of the study of IBD in both scientific and clinical communities. In addition to providing a reference that can be considered the most influential paper in inflammatory bowel disease, this work provides a reference for researchers and clinicians to become a citable paper in the field of inflammatory bowel disease research.

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