Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(4) 1467–1482

DOI: 10.1177/0300060519835974
journals.sagepub.com/home/imr
SAGE

The 100 most influential manuscripts on hepatocellular carcinoma: a bibliometric analysis

Ji Woong Hwang[1], Hanbaro Kim[2] and Dong Jin Lee[3]

Abstract

Objective: Citation analysis represents one of the best available methods to identify the most influential articles. This study aimed to identify and characterize the top 100 highly cited articles (T100) that focus on hepatocellular carcinoma and to reveal the trends in accomplishments within this field.

Methods: A search of the Thomson Reuters Web of Science citation indexing database was conducted using terms related to hepatocellular carcinoma. The T100 were selected and analyzed further based on the number of citations, authorship, year of publication, journal, country of origin, institution, and article type.

Results: *Hepatology* published the highest number of papers (n = 15), and the United States produced the highest number of contributions (n = 31). Barcelona University was the institution with the highest number of articles in the T100 (n = 9). The T100 articles included 35 observational studies, 13 randomized control studies, 25 basic research articles, 18 reviews, seven clinical guidelines, and two meta-analyses.

Conclusions: This is the first bibliometric study to identify the most influential papers in hepatocellular carcinoma research. This report presents major advances and changes in research regarding hepatocellular carcinoma and can serve as a guide for writing a citable article.

[1]Department of Surgery, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea
[2]Department of Surgery, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Korea
[3]Division of Precision Medicine, Department of Otolaryngology-Head and Neck Surgery, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea

Corresponding author:
Dong Jin Lee, Division of Precision Medicine, Department of Otolaryngology-Head and Neck surgery, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, 1 Singil-ro Yeongdeungpo-gu, Seoul 07441, Republic of Korea.
Email: leesurgery@gmail.com

Keywords
Hepatocellular carcinoma, bibliometrics, citations, authorship, publications, gastroenterology, liver neoplasms

Date received: 26 October 2018; accepted: 14 February 2019

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and is a leading cause of cancer death worldwide.[1] Numerous articles have been published regarding HCC in various fields, such as clinical pathology, clinical oncology, clinical radiology, and basic research. Through such efforts, great progress has been made in understanding and treating HCC. However, it is difficult to identify the most influential or important articles among the considerable number of publications.

Establishing a citation rank list can identify which published works have had the greatest intellectual influence.[2] For example, researchers with medical and surgical specialties have utilized citation rank analysis to identify the most influential articles in their fields, such as orthopedic surgery,[3] plastic surgery,[4] general surgery,[5] and oncology.[6] Notably, there is a need to determine the most influential research themes in the diagnosis and management of HCC. Additionally, there is a need to assemble a registry of the most cited papers. Although a comprehensive analysis of overall research trends in the past 10 years has been performed for HCC,[7] a wide-ranging bibliometric analysis of HCC research has not been performed in terms of the most influential papers in the field. Therefore, this study aimed to identify and characterize the top 100 highly cited articles (T100) that have focused on HCC and to highlight trends in accomplishments within this field.

Materials and methods

A search of the Thomson Reuters Web of Science citation indexing database was conducted for the period from 1 January 1983 to 11 October 2017 (the beginning of the search window was limited by the terms of our access to the database). The following search terms were used: "hepatocellular carcinoma," "hepatoma", "liver cancer," and "liver cell carcinoma." The search was conducted on a single day, 11 October 2017, to minimize adjustments to the number of citations during the search. The search strategy was limited to full manuscripts published in English, and the results were sorted by the number of citations, in accordance with the method initially developed by Paladugu and colleagues.[5] The final Web of Science database interrogation was performed jointly by two independent reviewers (HJW and KH) to ensure its relevance to HCC. The selected T100 articles were then evaluated further based on the following parameters: number of citations, authorship, year of publication, journal, country of origin, institution, and article type. Because a potential bias in this type of study is that older manuscripts may have a higher number of citations because of the extended period since publication, a "citation rate" was determined by dividing the number of citations by the number of years since publication.

Statistical analysis of the data—comprising one-way analysis of variance of the citation numbers of clinical research, review, and basic research articles—was performed

using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Differences with $P < 0.05$ were considered to be statistically significant.

Results

The Web of Science database search returned 71,639 full manuscript publications. Table 1 lists the 100 most frequently cited articles from the initial list. The number of citations ranged from 500 for Okuda et al.[8] ("Hepatocellular carcinoma: Recent progress") to 4,730 for Llovet et al.[9] ("Sorafenib in advanced hepatocellular carcinoma"). The mean number of citations for all articles was $1{,}002.67 \pm 718.57$. The citation rate was highest for the review article, "Management of hepatocellular carcinoma: An update," by Bruix et al (543.17).[10]

Thirteen authors had more than two first or last authorships in the T100 (Table 2). J. Llovet had the highest number of first authorships (n = 10; 17,452 citations), and J. Bruix had the highest number of last authorships (n = 9; 16,358 citations).

The selected T100 were published between 1983 and 2012, with half of the articles published from 2001 to 2010 (n = 54; see Figure 1). The year that yielded the highest number of T100 articles was 1999 (n = 10; 10,706 citations), followed by 2006 (n = 9; 8,013 citations). The oldest article featured in the T100 was published in 1983 by Yamada et al. ("Hepatic artery embolization in 120 patients with unresectable hepatoma"). The most recent article, published in 2012 by El-Serag et al.,[11] described an investigation of the epidemiology of viral hepatitis and HCC.

The T100 were published in 31 journals (Table 3). Although *Hepatology* had a lower 5-year impact factor than the *New England Journal of Medicine (NEJM)* (11.930 vs. 64.201), *Hepatology* published the most papers in the T100 (n = 15; 14,586 citations). *NEJM* generated the highest number of citations (n = 11; 17,105 citations).

The highest number of contributions was produced by groups in the United States (n = 31), followed by Japan (n = 17) and Spain (n = 16) (Figure 2). The University of Barcelona was the institution with the highest number of articles in the T100 (n = 9; 14,012 citations; Table 4).

The T100 articles included 35 observational studies, 25 basic research articles, 18 reviews, 13 randomized control studies, seven clinical guidelines, and two meta-analyses. Figure 3 shows the topical distribution of the T100 by 5-year periods from 1983 to 2015 (the first period is truncated to 1983-1985 because of the search constraints). After 2000, the proportion of observational studies declined, whereas the proportion of basic research studies increased.

We subdivided the T100 by article types: clinical research (n = 48), review article (n = 27), and basic research (n = 25). Although clinical research articles comprised approximately half of the T100, the mean number of citations was significantly higher for review articles than for other article types ($P = 0.010$; Figure 4).

Discussion

Bibliometric analysis identifies the most influential articles in the field during the past several decades, highlights contributions that have led to significant advances, and reveals current trends in the field. This type of analysis reveals key advancements and provides a useful perspective on historical developments in the field.[12] The top 100 highly cited articles worldwide have been published in various fields, such as cardiology,[13] neurosurgery,[14] endocrinology,[15] radiology,[16] and ophthalmology.[17] However, to the best of our knowledge, this study is the first bibliometric analysis

Table 1. The top 100 cited papers on HCC.

Rank	Article	Citations	Citation rate
1	Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378–390.	4730	525.56
2	Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334: 693–699.	3620	172.38
3	Bruix J, Sherman M. Management of hepatocellular carcinoma: An update. *Hepatology* 2011; 53: 1020–1022.	3259	543.17
4	Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. *J Hepatol* 2001; 35: 421–430.	2806	175.38
5	Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; 362: 1907–1917.	2783	198.79
6	El-Serag HB, Rudolph L. Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; 132: 2557–2576.	2706	270.6
7	El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; 340: 745–750.	2076	115.33
8	Cheng AL, Kang YK, Chen ZD, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10: 25–34.	2061	257.63
9	Lohmann V, Korner F, Koch JO, et al. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 1999; 285: 110–113.	2039	113.28
10	Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. *Lancet* 2002; 359: 1734–1739.	1792	119.47
11	Llovet JM, Lencioni R, Di Bisceglie AM, et al. EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2012; 56: 908–943.	1730	346
12	Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; 295: 65–73.	1636	148.73
13	Llovet JM, Bruix J, Barcelona Clinic Liver Cancer Group. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003; 37: 429–442.	1620	115.71
14	Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; 379: 1245–1255.	1609	321.8
15	Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. *Semin Liver Dis* 1999; 19: 329–338.	1525	84.72
16	El-Serag HB. Current concepts: hepatocellular carcinoma. *N Engl J Med* 2011; 365: 1118–1127.	1511	251.83

(continued)

Table 1. Continued.

Rank	Article	Citations	Citation rate
17	Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; 56: 918–928.	1432	44.75
18	Bosch FX, Ribes J, Diaz M, et al. Primary liver cancer: Worldwide incidence and trends. *Gastroenterology* 2004; 127: S5–S16.	1376	105.85
19	Hsu IC, Metcalf RA, Sun T, et al. Mutational hotspot in the p53 gene in human hepatocellular carcinomas. *Nature* 1991; 350: 427–428.	1362	52.38
20	Bressac B, Kew M, Wands J, et al. Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. *Nature* 1991; 350: 429–431.	1178	45.31
21	Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; 35: 1164–1171.	1161	77.4
22	Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006; 45: 529–538.	1137	103.36
23	Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997; 336: 1855–1859.	1111	55.55
24	Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: From genes to environment. *Nat Rev Cancer* 2006; 6: 674–687.	1105	100.45
25	Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; 33: 1394–1403.	1084	67.75
26	Kiyosawa K, Sodeyama T, Tanaka E, et al. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: Analysis by detection of antibody to hepatitis C virus. *Hepatology* 1990; 12: 671–675.	1062	39.33
27	Llovet JM, Fuster J, Bruix J, et al. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: Resection versus transplantation. *Hepatology* 1999; 30: 1434–1440.	1046	58.11
28	Saito I, Miyamura T, Ohbayashi A, et al. Hepatitis C virus infection is associated with the development of hepatocellular carcinoma. *Proc Natl Acad Sci U S A* 1990; 87: 6547–6549.	1030	38.15
29	Kota J, Chivukula RR, O'Donnell KA, et al. Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model. *Cell* 2009; 137: 1005–1017.	1017	127.13
30	Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. *Gastroenterology* 2004; 127: S35–S50.	1005	77.31
31	Lencioni R, Llovet JM. Modified RECIST (MRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; 30: 52–60.	983	140.43
32	Thorgeirsson SS, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet* 2002; 31: 339–346.	983	65.53

(continued)

Table 1. Continued.

Rank	Article	Citations	Citation rate
33	Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008; 100: 698–711.	973	108.11
34	Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer* 1988; 61: 1942–1956.	937	32.31
35	Naugler WE, Sakurai T, Kim S, et al. Gender disparity in liver cancer due to sex differences in MYD88-dependent IL-6 production. *Science* 2007; 317: 121–124.	928	92.8
36	El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; 142: 1264–1273.e1.	925	185
37	Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: Treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999; 210: 655–661.	925	51.39
38	Kim CM, Koike K, Saito I, et al. Hbx gene of hepatitis B virus induces liver cancer in transgenic mice. *Nature* 1991; 351: 317–320.	909	34.96
39	Moriya K, Fujie H, Shintani Y, et al. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. *Nat Med* 1998; 4: 1065–1067.	866	45.58
40	Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history from cryptogenic cirrhosis to of nonalcoholic steatohepatitis: Hepatocellular carcinoma. *Gastroenterology* 2002; 123: 134–140.	861	57.4
41	Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993; 328: 1797–1801.	857	35.71
42	Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; 27: 1485–1491.	825	103.13
43	Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; 24: 4293–4300.	786	71.45
44	Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: National surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. *Ann Intern Med* 1999; 131: 174–181.	761	42.28
45	Yamada R, Sato M, Kawabata M, et al. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* 1983; 148: 397–401.	756	22.24
46	de La Coste A, Romagnolo B, Billuart P, et al. Somatic mutations of the beta-catenin gene are frequent in mouse and human hepatocellular carcinomas. *Proc Natl Acad Sci U S A* 1998; 95: 8847–8851.	755	39.74
47	Nishiguchi S, Kuroki T, Nakatani S, et al. Randomized trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995; 346: 1051–1055.	752	34.18

(continued)

Table 1. Continued.

Rank	Article	Citations	Citation rate
48	Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002; 347: 168–174.	751	50.07
49	Livraghi T, Giorgio A, Marin G, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: Long-term results of percutaneous ethanol injection. *Radiology* 1995; 197: 101–108.	740	33.64
50	Liu L, Cao YC, Chen C, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 2006; 66: 11851–11858.	737	67
51	Murakami Y, Yasuda T, Saigo K, et al. Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. *Oncogene* 2006; 25: 2537–2545.	731	66.45
52	Livraghi T, Goldberg SN, Lazzaroni S, et al. Hepatocellular carcinoma: Radio-frequency ablation of medium and large lesions. *Radiology* 2000; 214: 761–768.	713	41.94
53	Bismuth H, Chiche L, Adam R, et al. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993; 218: 145–151.	706	29.42
54	Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002; 35: 519–524.	697	46.47
55	Colombo M, Defranchis R, Delninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991; 325: 675–680.	696	26.77
56	Bruix J, Barrera JM, Calvet X, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. *Lancet* 1989; 2: 1004–1006.	689	24.61
57	Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006; 243: 321–328.	681	61.91
58	Hoshida Y, Villanueva A, Kobayashi M, et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. *N Engl J Med* 2008; 359: 1995–2004.	660	73.33
59	Zender L, Spector MS, Xue W, et al. Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell* 2006; 125: 1253–1267.	656	59.64
60	Muller M, Strand S, Hug H, et al. Drug-induced apoptosis in hepatoma cells is mediated by the CD95 (APO-1/Fas) receptor/ligand system and involves activation of wild-type p53. *J Clin Invest* 1997; 99: 403–413.	655	32.75
61	Mazzoferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: A retrospective, exploratory analysis. *Lancet Oncol* 2009; 10: 35–43.	650	81.25
62	Yang ZF, Ho DW, Ng MN, et al. Significance of CD90(+) cancer stem cells in human liver cancer. *Cancer Cell* 2008; 13: 153–166.	646	71.78

(continued)

Table 1. Continued.

Rank	Article	Citations	Citation rate
63	Manghisi G, Elba S, Mossa A, et al. A new prognostic system for hepatocellular carcinoma: A retrospective study of 435 patients. *Hepatology* 1998; 28: 751–755.	642	33.79
64	Llovet JM, Bruix J. Molecular targeted therapies in hepatocellular carcinoma. *Hepatology* 2008; 48: 1312–1327.	641	71.22
65	Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: Randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003; 228: 235–240.	638	45.57
66	Wang J, Chenivesse X, Henglein B, et al. Hepatitis B virus integration in a cyclin A gene in a hepatocellular carcinoma. *Nature* 1990; 343: 555–557.	635	23.52
67	El-Serag H, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: An update. *Ann Intern Med* 2003; 139: 817–823.	631	45.07
68	El-Serag HB. Hepatocellular carcinoma: Recent trends in the United States. *Gastroenterology* 2004; 127: S27–S34.	628	48.31
69	Bosch FX, Ribes J, Borras J. Epidemiology of primary liver cancer. *Semin Liver Dis* 1999; 19: 271–285.	616	34.22
70	Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: Rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999; 29: 62–67.	612	34
71	Colombo M, Kuo G, Choo QL, et al. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet* 1989; 2: 1006–1008.	611	21.82
72	Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: A weighty connection. *Hepatology* 2010; 51: 1820–1832.	604	86.29
73	Benbrook D, Lernhardt E, Pfahl M. A new retinoic acid receptor identified from a hepatocellular carcinoma. *Nature* 1988; 333: 669–672.	599	20.66
74	El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; 126: 460–468.	596	45.85
75	Jonas S, Bechstein WO, Steinmuller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001; 33: 1080–1086.	590	36.88
76	Fong YM, Sun RL, Jarnagin W, et al. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg* 1999; 229: 790–799.	585	32.5
77	Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; 130: 417–422.	576	44.31

(continued)

Table 1. Continued.

Rank	Article	Citations	Citation rate
78	Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and date phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 2003; 38: 200–207.	574	41
79	Gripon P, Rumin S, Urban S, et al. Infection of a human hepatoma cell line by hepatitis B virus. *Proc Natl Acad Sci U S A* 2002; 99: 15655–15660.	570	38
80	Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010; 33: 41–52.	568	81.14
81	Oberti F, Ruget O, Cales P, et al. Comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995; 332: 1256–1261.	561	25.5
82	Chisari FV, Klopchin K, Moriyama T, et al. Molecular pathogenesis of hepatocellular carcinoma in hepatitis B virus transgenic mice. *Cell* 1989; 59: 1145–1156.	556	19.86
83	Lee JS, Heo J, Libbrecht L, et al. A novel prognostic subtype of human hepatocellular carcinoma derived from hepatic progenitor cells. *Nat Med* 2006; 12: 410–416.	544	49.45
84	Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology* 2008; 47: 82–89.	543	60.33
85	Takayama T, Sekine T, Makuuchi M, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: A randomised trial. *Lancet* 2000; 356: 802–807.	541	31.82
86	El-Serag HB, Marrero JA, Rudolph L, et al. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 2008; 134: 1752–1763.	538	59.78
87	Gramantieri L, Ferracin M, Fornari F, et al. CyclinG1 is a target of miR-122a, a microRNA frequently down-regulated in human hepatocellular carcinoma. *Cancer Res* 2007; 67: 6092–6099.	535	53.5
88	Muto Y, Moriwaki H, Ninomiya M, et al. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. *N Engl J Med* 1996; 334: 1561–1567.	532	25.33
89	Yang JD, Roberts LR. Hepatocellular carcinoma: A global view. *Nat Rev Gastroenterol Hepatol* 2010; 7: 448–458.	530	75.71
90	Ye QH, Qin LX, Forgues M, et al. Predicting hepatitis B virus-positive metastatic hepatocellular carcinomas using gene expression profiling and supervised machine learning. *Nat Med* 2003; 9: 416–423.	525	30.88
91	Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: A retrospective and nationwide survey in Japan. *Hepatology* 2000; 32: 1224–1229.	525	37.5

(continued)

Table 1. Continued.

Rank	Article	Citations	Citation rate
92	Yamashita T, Ji JF, Budhu A, et al. Epcam-positive hepatocellular carcinoma cells are tumor-initiating cells with stem/progenitor cell features. *Gastroenterology* 2009; 136: 1012–1024.	524	65.5
93	Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: Toward zero hospital deaths. *Ann Surg* 1999; 229: 322–330.	521	28.94
94	Plymate SR, Matej LA, Jones RE, et al. Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. *J Clin Endocrinol M*etab 1988; 67: 460–464.	520	17.93
95	Gao Q, Qiu SJ, Fan J, et al. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. *J Clin Oncol* 2007; 25: 2586–2593.	518	51.8
96	Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005; 129: 122–130.	513	42.75
97	Chen X, Cheung ST, So S, et al. Gene expression patterns in human liver cancers. *Mol Biol Cell* 2002; 13: 1929–1939.	510	34
98	Yoshikawa H, Matsubara K, Qian GS, et al. SOCS-1, a negative regulator of the JAK/STAT pathway, is silenced by methylation in human hepatocellular carcinoma and shows growth-suppression activity. *Nat Genet* 2001; 28: 29–35.	509	31.81
99	Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010; 4: 439–474.	505	72.14
100	Okuda K. Hepatocellular carcinoma: Recent progress. *Hepatology* 1992; 15: 948–963.	500	20

Table 2. First and last authors with multiple articles in the top 100.

Rank	Author	First position	Last position	Total articles
1	Bruix, J	4	9	13
2	Llovet, J	10	2	12
3	El-Serag, H	8	0	8
4	Livraghi, T	4	0	4
5	Omata, M	1	2	3
6	Bosch, F	2	0	2
6	Chen, CJ	1	1	2
6	Colombo, M	2	0	2
6	Fan, ST	1	1	2
6	Lencioni, R	1	1	2
6	Okuda, K	2	0	2
6	Yamada, R	1	1	2
6	Gazelle, G	0	2	2

of the most influential citations regarding HCC.

The number of citations of an article depends partly on when the article was published, as citations accumulate over time. However, with the exception of the 2011 to 2015 period, the number of articles included in the T100 tended to increase for newer articles; thus, more than half of the articles in our study were published between 2001 and 2010. These findings are consistent with those of other recent bibliometric analyses.[12,13,17] The results demonstrate that new articles with novel discoveries and advanced technologies continue to be published, and that newer articles receive more citations than previous articles.

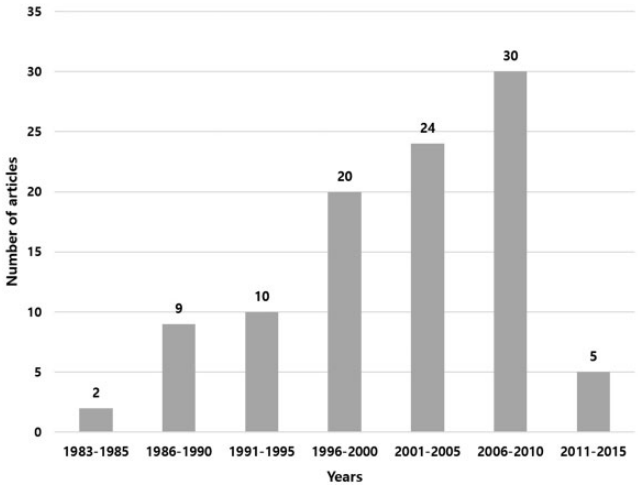

Figure 1. Numbers of publications stratified by 5-year intervals from 1983 to 2015.

The leading article by Llovet et al.[9] described a multicenter, randomized control study on sorafenib for treatment of advanced HCC, which may be the most important advancement in medical management of HCC. Some bibliometric studies have reported that journals with high impact factors, such as *NEJM* or *Nature*, were the leading journals within their respective fields.[18–20] However, we found that *Hepatology* and *Gastroenterology* were the most productive journals, despite their relatively low impact factors; indeed, they published 15 and 10 articles in the T100, respectively. This result highlights a growing trend in which highly influential articles are published in specialized journals, and are not limited to the most well-known general medical journals.

Although the United States was the most productive country in terms of research regarding HCC, most of the top productive institutions were evenly distributed among other countries, such as Japan, Spain, and Italy. Of note, countries within East Asia produced more than one-quarter of the T100 articles, in contrast to the trend reported in other bibliometric analyses. These countries had a particularly high prevalence of viral hepatitis and subsequent occurrence of HCC.[21] The high prevalence of HCC led to elevated production of influential studies, similar to the relationship with regional disease rates shown in a bibliometric analysis of influential studies regarding gastric cancer.[22] According to a recent bibliometric analysis,[7] China contributed the most publications regarding overall HCC research in recent decades, although it was the fifth country in terms of T100 articles in the present study. Because of the high prevalence of HCC in China, extensive research funding has been used to study diagnosis and treatment of HCC, such that China has shown considerable progress in HCC research.

Since the year 2000, the proportion of clinical research studies (e.g., observational studies and randomized control trials) has gradually decreased, relative to overall HCC-related publications, whereas the proportions of basic research studies, clinical guidelines, and meta-analyses have increased (Figure 3). This phenomenon suggests that the accumulation of knowledge and experience related to HCC have led to

Table 3. Journals with four or more articles in the top 100.

Journal title	Impact factor 2016	5-year impact factor	Number of manuscripts in the top 100	Number of citations
Hepatology	13.246	11.930	15	14586
New England Journal of Medicine	75.406	64.201	11	17105
Gastroenterology	18.392	16.825	10	9672
Lancet	47.831	48.082	7	8777
Nature	40.137	43.769	5	4683
Radiology	7.296	7.648	5	3772
Journal of Hepatology	12.486	11.230	4	6247
Annals of Surgery	8.98	9.410	4	2493

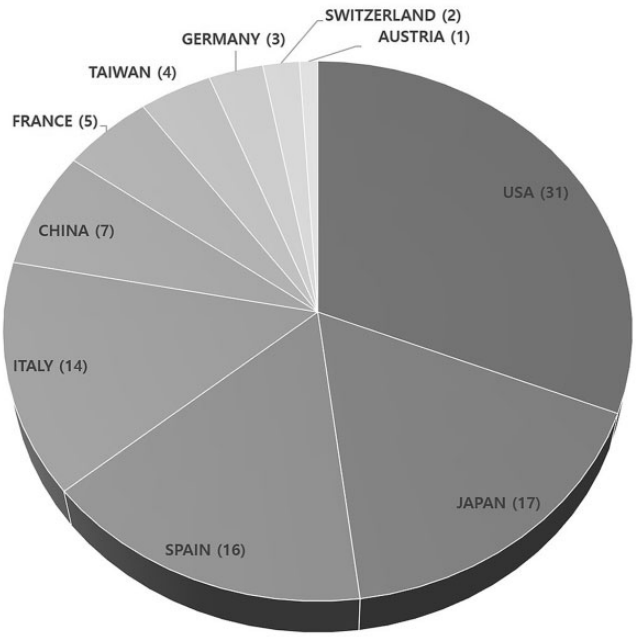

Figure 2. Distribution of the top 100 articles by country of origin from 1983 to 2015.

additional publications comprising comprehensive analyses, rather than intermittent clinical trials. In addition, the remarkable developments in molecular biology and genetics with regard to HCC have facilitated publication of basic research studies in high impact journals: *Nature*, *Nature Medicine*, *Cancer Cell*, and *Science*. Nevertheless, clinical studies comprise one-half of publications in the T100, indicating that clinical research continues to attract the interest of researchers in the field.[23]

In bibliometric analysis for other gastrointestinal cancers, there has been increasing publication of articles regarding basic cancer research, such as cancer genetics, chemotherapy regimens, and monoclonal antibody. However, one-half of the top

Table 4. Institutions with three or more articles in the top 100.

Institution	Number of publications in top 100	Total number of citations
University of Barcelona	9	14,012
The University of Tokyo	6	3,760
National Cancer Institute	5	3,401
National Taiwan University	4	5,559
Ospedale Civile	4	2,921
University of Hong Kong	4	2,838
Hospital Clinic of Barcelona	3	7,323
Houston Veterans Affairs Medical Center	3	1,855

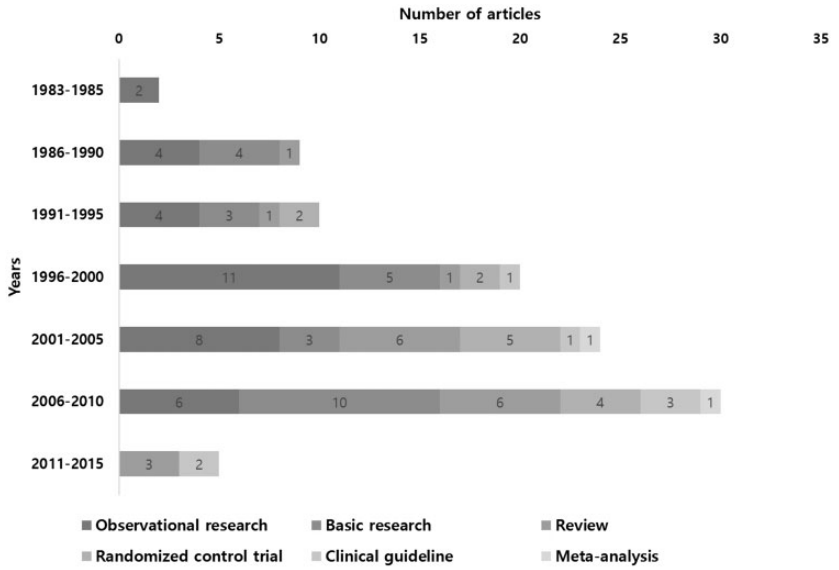

Figure 3. Publication trends for specific article types stratified by 5-year intervals from 1983 to 2015.

100 HCC studies comprised clinical studies, such that there was a relative lack of basic research studies on HCC, compared with studies of other gastrointestinal malignancies. Therefore, further developments involving chemotherapeutic agents and basic cancer research are needed to improve the survival rate of HCC.

There are various treatment modalities for HCC: liver transplantation, hepatectomy, radiofrequency ablation, transarterial chemoembolization, and chemotherapy. The top 10 of the T100 primarily included studies involving treatment modalities of HCC ($n = 6$). Although the surgical method for resolution of HCC is regarded as the preferred approach,[24] articles describing non-surgical treatments were more frequently represented in the top 10, as well as the overall T100. This may be due to the increasing need for treatment of unresectable and recurrent HCC. This

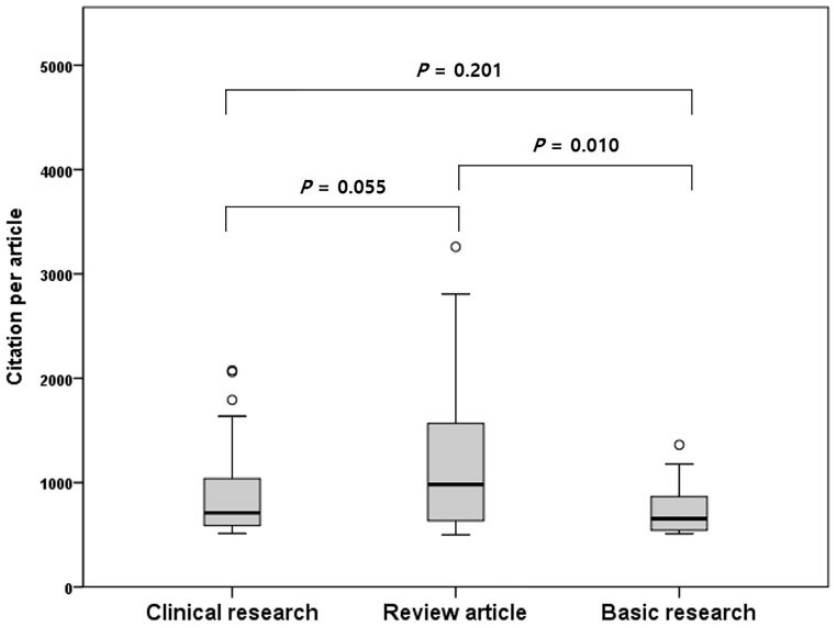

Figure 4. Bar graph showing the number of citations (mean ± standard deviation) for the top 100 articles from 1983 to 2015, stratified by article type (clinical research, review article, basic research). Black bar, mean; whiskers, standard deviation; box, 95% confidence interval.

trend is consistent with that described in bibliometric analyses regarding other gastrointestinal cancers.[12,22,25] Among the top 10 articles, two described randomized control trials of the effects of sorafenib on HCC; one of these two was the most highly cited, and was published in *NEJM*.

The main limitation of this manuscript is the potential for several types of bias, which may have affected the results. Disproportionate or inappropriate citations may result from institutional bias, language bias, self-citation, powerful person bias, in-house bias, or the deliberate omission of citations for a variety of reasons, including competition.[26] Moreover, older articles may receive more citations due to the relative length of time since their publication. To correct this bias, the citation rate was analyzed, in which the number of citations was divided by the number of years since publication. Despite these attempts, the lead time for publication of citing articles may have resulted in under-representation of more recent articles in our study.[22] Another limitation is the inclusion of only the first and senior authors and the institutions of the first author. Thus, several authors in the T100 may have contributed to multiple manuscripts, although in a lesser role than that of first or senior author.

Conclusion

To our knowledge, this is the first bibliometric study to identify the most influential papers in HCC research. This report presents major advances and changes in research regarding HCC and can serve as a guide for writing a citable article.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research was supported by Hallym University Research Fund 2018 (HURF-2018-17).

ORCID iD

Ji Woong Hwang http://orcid.org/0000-0001-8533-4461

References

1. Chang L, Wang Y, Zhang J, et al. The best strategy for HCC patients at each BCLC stage: a network meta-analysis of observational studies. *Oncotarget* 2017; 8: 20418–20427.
2. Murray MR, Wang T, Schroeder GD, et al. The 100 most cited spine articles. *Eur Spine J* 2012; 21: 2059–2069.
3. Kelly JC, Glynn RW, O'Briain DE, et al. The 100 classic papers of orthopaedic surgery: a bibliometric analysis. *J Bone Joint Surg Br* 2010; 92: 1338–1343.
4. Loonen MP, Hage JJ and Kon M. Plastic Surgery Classics: characteristics of 50 top-cited articles in four Plastic Surgery Journals since 1946. *Plast Reconstr Surg* 2008; 121: 320e–327e.
5. Paladugu R, Schein M, Gardezi S, et al. One hundred citation classics in general surgical journals. *World J Surg* 2002; 26: 1099–1105.
6. Tas F. An analysis of the most-cited research papers on oncology: which journals have they been published in? *Tumour Biol* 2014; 35: 4645–4649.
7. Miao Y, Zhang Y and Yin L. Trends in hepatocellular carcinoma research from 2008 to 2017: a bibliometric analysis. *PeerJ* 2018; 6: e5477.
8. Okuda K. Hepatocellular carcinoma: recent progress. *Hepatology* 1992; 15: 948–963.
9. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378–390.
10. Bruix J, Sherman M and American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53: 1020–1022.
11. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; 142: 1264–1273.
12. Li Q and Jiang Y. Top classic citations in pancreatic cancer research. *World J Surg Oncol* 2016; 14: 298.
13. Usman MS, Siddiqi TJ, Khan MS, et al. A scientific analysis of the 100 citation classics of valvular heart disease. *Am J Cardiol* 2017; 120: 1440–1449.
14. Nasir SAR, Gilani JA, Fatima K, et al. Top 100 most-cited articles on spontaneous intracerebral hemorrhage: a bibliometric analysis. *World Neurosurg* 2018; 110: 445–449.e6.
15. Tian J, Li M, Lian F, et al. The hundred most-cited publications in microbiota of diabetes research: a bibliometric analysis. *Medicine (Baltimore)* 2017; 96: e7338.
16. Hong SJ, Lim KJ, Hwang HJ, et al. The 100 top-cited articles in pulmonary imaging: a bibliometric analysis. *J Thorac Imaging* 2017; 32: 198–202.
17. Schargus M, Kromer R, Druchkiv V, et al. The top 100 papers in dry eye - A bibliometric analysis. *Ocul Surf* 2017; 16: 180–190.
18. Shuaib W, Acevedo JN, Khan MS, et al. The top 100 cited articles published in emergency medicine journals. *Am J Emerg Med* 2015; 33: 1066–1071.
19. Khan MS, Ullah W, Riaz IB, et al. Top 100 cited articles in cardiovascular magnetic resonance: a bibliometric analysis. *J Cardiovasc Magn Reson* 2016; 18: 87.
20. Siddiqi TJ, Usman MS, Khan MS, et al. The 100 most influential papers in the field of thrombolytic therapy: a bibliometric analysis. *Am J Cardiovasc Drugs* 2017; 17: 319–333.
21. Sartorius K, Sartorius B, Aldous C, et al. Global and country underestimation of hepatocellular carcinoma (HCC) in 2012 and its implications. *Cancer Epidemiol* 2015; 39: 284–290.
22. Powell AG, Hughes DL, Wheat JR, et al. The 100 most influential manuscripts in gastric cancer: a bibliometric analysis. *Int J Surg* 2016; 28: 83–90.
23. Ahmad SS, Evangelopoulos DS, Abbasian M, et al. The hundred most-cited publications in orthopaedic knee research. *J Bone Joint Surg Am* 2014; 96: e190.

24. Benson AB, Abrams TA, Ben-Josef E, et al. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *J Natl Compr Canc Netw* 2009; 7: 305–391.
25. Wrafter PF, Connelly TM, Khan J, et al. The 100 most influential manuscripts in colorectal cancer: a bibliometric analysis. *Surgeon* 2016; 14: 327–336.
26. Garfield E. Journal impact factor: a brief review. *CMAJ* 1999; 161: 979–980.