

Top 100 Cited Articles in the Field of Hepatocellular Carcinoma: A Bibliometric Analysis

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ABSTRACT

AIM: Bibliometric analyses are used by funding agencies and researchers to identify major contributors to scientific progress. Citation classics have been identified in many gastrointestinal malignancies, but not yet for hepatocellular carcinoma (HCC). Thus we sought to analyze the 100 most cited articles in this field.

MATERIALS AND METHODS: The Scopus database was searched by two reviewers for articles concerning HCC. The 100 top cited papers were analyzed by topic, journal, author, year and institution.

RESULTS: The 100 most-cited articles in HCC were published between 1954 and 2012, with the most articles ($n = 29$) published

in period 2006-2010. The total number of citations of these articles ranged from 618-4,833 (median = 934.5) citations. These articles originated from 21 countries, with nearly half from the USA ($n = 49$), followed by Spain and Italy ($n = 19$). The University of Barcelona, Spain contributed the most articles ($n = 13$). *Hepatology* contributed the greatest number of articles ($n = 19$), with *New England Journal of Medicine* having the greatest number of citations ($n = 21,276$). Seventy-five of the top 100 papers were original articles; most of these focused on genetics/pathophysiology ($n = 27$) or management ($n = 24$).

CONCLUSION: Our analysis serves as a reference for the most highly cited works in HCC and characterizes research trends in the field.

Key words: Bibliometrics; Citation classics; Liver cancer; Hepatocellular carcinoma; Scientometrics

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, and in 2015 it ranked as the sixth most common neoplasm and the fourth leading cause of cancer-related mortality^[1]. Given this high global disease burden, it can be appreciated that significant resources are devoted to research in HCC. The association of several modifiable risk factors such as viral hepatitis infections and alcoholic liver disease with hepatocarcinogenesis has generated strong interest in preventive screening research and implementation. In addition, there is an urgent and expanding role for novel molecular therapies like sorafenib in the management of this chemo-resistant tumor. The promise of precision medicine in HCC has focused much research on genomic profiling to identify prognostic markers and targets for drug therapy.

With increasing emphasis on evidence-based medicine, recent years have seen a rise in the number of research publications^[2]. Bibliometric methods of analyzing research meta-data can provide useful information to funding agencies, federal policymakers and individual researchers and clinicians. Citation analysis can also identify which areas should be prioritized by future research. For physicians, a list of citation classics enables them to efficiently navigate landmark developments in their field.

Despite criticism, citation rate and impact factor metrics are widely used to assess the scholarly impact of a scientific manuscript^[3, 4]. Many medical and surgical specialties have utilized bibliometric techniques to identify their citation classics and characterize research trends, including several gastrointestinal malignancies^[5-11]. However to our knowledge no such analysis has yet been published on HCC. The objective of our study was to present the 100 top cited articles and to gain insight on the evolution of HCC research.

METHODS

In January 2018, two independent researchers (NA and RS) searched the Scopus database (www.scopus.com) for citations of articles published on HCC. As compared to PubMed, Web of Science or Google Scholar, Scopus is known to have a greater coverage where scientific publications are concerned^[12]. In order to broaden the results, all article types, non-human studies and studies without abstract availability were included. No time restriction was applied and all the journals in the database were included in the search. Articles with their main focus on HCC, epidemiology, carcinogenesis, management, surgery and chemotherapy were included.

Our primary search phrases included “liver cancer”, “hepatocellular cancer”, “hepatic cancer”, “hepatocarcinogenesis” and “HCC”. All these terms were also searched using “carcinoma”, “neoplasm”, “tumor” and “malignancy” and their plural forms. All individual key phrases were searched for in the title, keywords and abstract.

The returned dataset was strictly related to HCC. Abstracts of all articles were thoroughly analyzed for relevance to the topic according to the inclusion and exclusion criteria, independently by both reviewers. Abstracts were obtained from other search engines if they were not available on Scopus and similarly analyzed for relevance. The top 100 selected articles were ordered using “cited by” option. A final list was made after comparing both reviewers’ lists. A difference of 5.5% was observed between the lists. Articles were only included after consensus and agreement of both reviewers.

The final list was exported to Microsoft Excel 2016. The list was analyzed for the following: article title, author, author affiliations, number of authors, journal, total citations, year of publication, citations per year, institution and country of origin of the first author. H index and affiliations of authors were obtained from their Scopus profiles. We calculated the median and inter-quartile range (IQR) for total number of citations and citations per year, as our data were not expected to be normally distributed. Thomson Reuters’ Journal Citation Reports 2017 was used to obtain the journal’s impact factor. Tables and charts were made using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA). Pearson product-moment correlation test was applied to determine the correlation between journal impact factor and the number of papers of that journal in the top 100 list, using IBM SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 22. A *p* value of <0.05 was considered significant. No ethics approval was required for this study as all data are publicly available.

RESULTS

1. Citation Count and Citations per Year

Table 1 shows the top 100 cited articles in the field of HCC, along with their total citations, citation per year and rank according to total citations and citation per year. The citation count ranged from 618-4,833 for these 100 articles, with median of 934.5 (IQR = 582.5). The citations of all the articles sum up to 125,615, with approximately 3% (*n* = 3762) being self-citations. The number of citations per year ranged from 14.6 to 579.4. The median number of citations per year was 62.8 (IQR = 65.0).

2. Year of Publication, Origin and Authorship

The top ten articles were published after 1996. The 100 most cited articles were published between 1954 and 2012. During this 58 year span, the largest number of these articles (*n* = 29) were published in the 5-year period from 2006 to 2010, followed by 2001-2005 (*n* = 24) as shown in Figure 1. During 2006-2010, 5 articles out of the 29 published discussed sorafenib. In contrast, out of the 40 articles published during 1993-2003, 19 articles were based on HCC treatment; 10 articles from the aforementioned 19 were about chemoembolization and radiofrequency ablation, whereas 5 explored liver transplantation and resection. The remaining 4 covered other miscellaneous aspects of HCC treatment.

Twenty-one different countries contributed to the 100 most cited articles. Nearly half of the articles originated from USA (*n* = 49), followed by Italy and Spain with an equal number of articles (*n* = 19). Thirty-one articles had authors from more than one country. One article from the list had unidentified authorship nationality (Figure 2).

A total of 808 authors contributed to these 100 articles. The number of authors for each article ranged from 1 to 49, with each paper having a median of 7 authors (IQR = 7.25). Table 2 lists all the authors with 5 or more publications in top 100 cited articles along with their H-index. Jordi Bruix coauthored the greatest number of articles (*n* = 19) followed by Josep M Llovet (*n* = 17), and Hashem B El-Serag (*n* = 7).

3. Journal and Institutional Affiliations

The 100 most cited articles were published in 28 different journals, with top 5 producing nearly half of the articles (*n* = 49). These five journals included (1) *Hepatology* (2) *New England Journal of Medicine* (3) *Gastroenterology* (4) *The Lancet*, and (5) *Nature*. *Hepatology* published the most articles (*n* = 19), but *New England Journal of Medicine* generated the largest number of total citations (21,276) with 15 papers. The median impact factor for these 28 journals was 15.2 (range = 2.19-72.4). Thirty-five articles in our list were published in journals having impact factors of 30.0 or above. We found no significant correlation between the impact factor of a journal and the number of articles of that journal in the top 100 list (*p* = 0.146). Journals with more than 2 articles in top 100 are shown in Table 3.

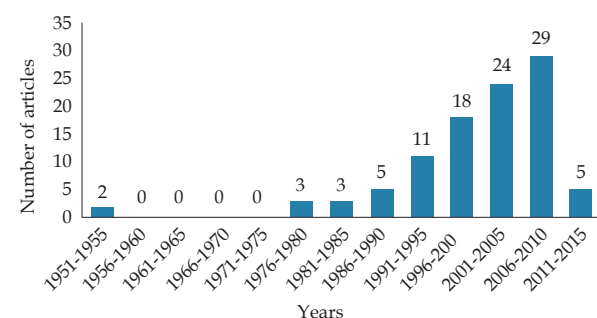


Figure 1 Number of publications in each 5-year interval.

Table 1 Top 100 cited articles, their total citations, citations per year and rank according to citations per year.

Rank	Article	Number of total citations	Average citations per year	Rank by average citations per year
1	Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. <i>New Engl J Med.</i> 2008; 359(4): 378-90.	4833	483	2
2	Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. <i>New Engl J Med.</i> 1996; 334(11): 693-9.	4226	192.1	10
3	Bruix J, Sherman M. Management of hepatocellular carcinoma. <i>Hepatology.</i> 2005; 42(5): 1208-36.	4035	310.4	5
4	Bruix J, Sherman M. Management of hepatocellular carcinoma: An update. <i>Hepatology.</i> 2011; 53(3): 1020-2.	3846	579.4	1
5	Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. <i>Lancet.</i> 2003; 362(9399): 1907-17.	3140	209.3	9
6	El-Serag HB, Rudolph KL. Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis. <i>Gastroenterology.</i> 2007; 132(7): 2557-76.	3106	282.4	6
7	Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the barcelona-2000 EASL conference. <i>J Hepatol.</i> 2001; 35(3): 421-30.	3019	177.6	12
8	El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. <i>New Eng J Med.</i> 1999; 340(10): 745-50.	2517	132.5	17
9	Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, 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. <i>Lancet Oncol.</i> 2009; 10(1): 25-34.	2412	268	7
10	European Association for the Study of the L, Llovet JM, Ducreux M, Lencioni R, Di Bisceglie AM, Galle PR, et al. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. <i>J Hepatol.</i> 2012; 56(4): 908-43.	2322	387	3
11	Edmondson HA, Steiner PE. Primary carcinoma of the liver. A study of 100 cases among 48,900 necropsies. <i>Cancer.</i> 1954; 7(3): 462-503.	2256	35.6	85
12	Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. <i>Lancet.</i> 2002; 359(9319): 1734-9.	2123	132.7	16
13	Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. <i>Hepatology.</i> 2003; 37(2): 429-42.	1928	128.5	18
14	Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. <i>Lancet.</i> 2012; 379(9822): 1245-55.	1920	320	4
15	Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA Level. <i>J Am Med Assoc.</i> 2006; 295(1): 65-73.	1892	157.7	14
16	Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. <i>Semin Liver Dis.</i> 1999; 19(3): 329-37.	1803	94.9	29
17	Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. <i>Lancet.</i> 1981; 2(8256): 1129-32.	1767	47.8	64
18	El-Serag HB. Hepatocellular carcinoma. <i>New Eng J Med.</i> 2011; 365(12): 1118-27.	1755	250.7	8
19	Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 Regulates Expression of the PTEN Tumor Suppressor Gene in Human Hepatocellular Cancer. <i>Gastroenterology.</i> 2007; 133(2): 647-58.	1726	156.9	13
20	Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: Worldwide incidence and trends. <i>Gastroenterology.</i> 2004; 127(SUPPL.): S5-S16.	1687	120.5	20
21	Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RTP, et al. Randomized controlled trial of transarterialLipiodol chemoembolization for unresectable hepatocellular carcinoma. <i>Hepatology.</i> 2002; 35(5): 1164-71.	1670	104.4	26
22	Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, et al. NF-kappaB functions as a tumour promoter in inflammation-associated cancer. <i>Nature.</i> 2004; 431(7007): 461-6.	1634	116.7	21
23	Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment study of 850 patients. <i>Cancer.</i> 1985; 56(4): 918-28.	1559	47.2	67
24	Knowles BB, Howe CC, Aden DP. Human hepatocellular carcinoma cell lines secrete the major plasma proteins and hepatitis B surface antigen. <i>Science.</i> 1980; 209(4455): 497-9.	1368	36	84
25	Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. <i>New Engl J Med.</i> 1997; 336(26): 1855-9.	1351	64.3	49
26	Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. <i>J Hepatol.</i> 2006; 45(4): 529-38.	1322	110.2	22
27	Hsu IC, Metcalf RA, Sun T, Welsh JA, Wang NJ, Harris CC. Mutational hot spot in the p53 gene in human hepatocellular carcinomas. <i>Nature.</i> 1991; 350(6317): 427-8.	1282	47.5	65
28	Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. <i>Gastroenterology.</i> 2004; 127(SUPPL.): S35-S50.	1275	91.1	31
29	Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. <i>Hepatology.</i> 2001; 33(6): 1394-403.	1273	74.9	37
30	Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: Resection versus transplantation. <i>Hepatology.</i> 1999; 30(6): 1434-40.	1249	65.7	48
31	Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, et al. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. <i>Nature.</i> 2007; 445(7128): 656-60.	1205	109.5	23
32	Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: From genes to environment. <i>Nat Rev Cancer.</i> 2006; 6(9): 674-87.	1198	99.8	27
33	Kota J, Chivukula RR, O'Donnell KA, Wentzel EA, Montgomery CL, Hwang HW, et al. Therapeutic microRNA Delivery Suppresses Tumorigenesis in a Murine Liver Cancer Model. <i>Cell.</i> 2009; 137(6): 1005-17.	1150	127.8	19
34	El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. <i>Gastroenterology.</i> 2012; 142(6): 1264-73.e1.	1147	191.2	11

Rank	Article	Number of total citations	Average citations per year	Rank by average citations per year
35	Lencioni R, Llovet JM. Modified recist (mRECIST) assessment for hepatocellular carcinoma. <i>Semin Liver Dis.</i> 2010; 30(1): 52-60.	1147	143.4	15
36	Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: Treatment with radio-frequency ablation versus ethanol injection. <i>Radiology.</i> 1999; 210(3): 655-61.	1112	58.5	52
37	Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, et al. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: Analysis by detection of antibody to hepatitis C virus. <i>Hepatology.</i> 1990; 12(4): 671-5.	1110	39.6	76
38	Bressac B, Kew M, Wands J, Ozturk M. Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. <i>Nature.</i> 1991; 350(6317): 429-31.	1099	40.7	72
39	Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. <i>J Natl Cancer Inst.</i> 2008; 100(10): 698-711.	1089	108.9	24
40	Thorgeirsson SS, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. <i>Nat Genet.</i> 2002; 31(4): 339-46.	1078	67.4	45
41	Bugianesi E, Leone N, Vanni E, Rizzetto M, Brunello F, Carucci P, et al. Expanding the natural history of nonalcoholic steatohepatitis: From cryptogenic cirrhosis to hepatocellular carcinoma. <i>Gastroenterology.</i> 2002; 123(1): 134-40.	1066	66.6	47
42	Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. <i>Cancer.</i> 1988; 61(10): 1942-56.	1040	34.7	89
43	Saito I, Miyamura T, Ohbayashi A, Harada H, Katayama T, Kikuchi S, et al. Hepatitis C virus infection is associated with the development of hepatocellular carcinoma. <i>Proc Natl AcadSci USA.</i> 1990; 87(17): 6547-9.	1038	37.1	81
44	Naugler WE, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, et al. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. <i>Science.</i> 2007; 317(5834): 121-4.	1035	94.1	30
45	Moriya K, Fujie H, Shintani Y, Yotsuyanagi H, Tsutsumi T, Ishibashi K, et al. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. <i>Nat Med.</i> 1998; 4(9): 1065-7.	990	49.5	63
46	Nakabayashi H, Taketa K, Miyano K, Yamane T, Sato J. Growth of human hepatoma cells lines with differentiated functions in chemically defined medium. <i>Cancer Res.</i> 1982; 42(9): 3858-63.	976	27.1	94
47	Curley SA, Izzo F, Delrio P, Ellis LM, Granchi J, Vallone P, et al. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: Results in 123 patients. <i>Ann Surg.</i> 1999; 230(1): 1-8.	961	50.6	61
48	Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. <i>J ClinOncol.</i> 2009; 27(9): 1485-91.	953	105.9	25
49	Kim CM, Koike K, Saito I, Miyamura T, Jay G. HBx gene of hepatitis B virus induces liver cancer in transgenic mice. <i>Nature.</i> 1991; 351(6324): 317-20.	948	35.1	88
50	Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. <i>J ClinOncol.</i> 2006; 24(26): 4293-300.	936	78	36
51	Breedis C, Young G. The blood supply of neoplasms in the liver. <i>Am J Pathol.</i> 1954; 30(5): 969-77.	933	14.6	100
52	Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: Complications encountered in a multicenter study. <i>Radiology.</i> 2003; 226(2): 441-51.	931	62.1	51
53	Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk Factors for Hepatocellular Carcinoma among Patients with Chronic Liver Disease. <i>New Engl J Med.</i> 1993; 328(25): 1797-801.	929	37.2	80
54	Aden DP, Fogel A, Plotkin S, Damjanov I, Knowles BB. Controlled synthesis of HBsAg in a differentiated human liver carcinoma-derived cell line [15]. <i>Nature.</i> 1979; 282(5739): 615-6.	912	23.4	97
55	Manghisi G, Elba S, Mossa A, Giorgio A, Aloisio V, Perrotta A, et al. A new prognostic system for hepatocellular carcinoma: A retrospective study of 435 patients. <i>Hepatology.</i> 1998; 28(3): 751-5.	904	45.2	69
56	Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata 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. <i>Ann Intern Med.</i> 1999; 131(3): 174-81.	896	47.2	68
57	Yang HL, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. <i>New Engl J Med.</i> 2002; 347(3): 168-74.	879	54.9	55
58	Livraghi T, Giorgio A, Marin G, Salmi A, De Sio I, Bolondi L, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: Long-term results of percutaneous ethanol injection. <i>Radiology.</i> 1995; 197(1): 101-8.	869	37.8	79
59	Tobe T, Endo Y, Hattori N, Ichida F, Mizumoto R, Mori W, et al. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. <i>Ann Surg.</i> 1990; 211(3): 277-87.	867	31	91
60	Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Ierace T, Solbiati L, et al. Hepatocellular carcinoma: Radio-frequency ablation of medium and large lesions. <i>Radiology.</i> 2000; 214(3): 761-8.	851	47.3	66
61	Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. <i>Cancer Res.</i> 2006; 66(24): 11851-8.	847	70.6	42
62	Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, et al. Randomised trial of effects of interferon- α on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. <i>Lancet.</i> 1995; 346(8982): 1051-5.	844	36.7	82
63	De La Coste A, Romagnolo B, Billuart P, Renard CA, Buendia MA, Soubrane O, et al. Somatic mutations of the β -catenin gene are frequent in mouse and human hepatocellular carcinomas. <i>Proc Natl AcadSci USA.</i> 1998; 95(15): 8847-51.	828	41.4	71
64	Murakami Y, Yasuda T, Saigo K, Urashima T, Toyoda H, Okanou T, et al. Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. <i>Oncogene.</i> 2006; 25(17): 2537-45.	824	68.7	44
65	Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. <i>Hepatology.</i> 2002; 35(3): 519-24.	823	51.4	58
66	Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. <i>Ann Surg.</i> 2006; 243(3): 321-8.	807	67.3	46
67	El-Serag HB. Hepatocellular carcinoma: Recent trends in the United States. <i>Gastroenterology.</i> 2004; 127(SUPPL.): S27-S34.	797	56.9	54

Rank	Article	Number of total citations	Average citations per year	Rank by average citations per year
68	Bosch FX, Ribes J, Borràs J. Epidemiology of primary liver cancer. <i>Semin Liver Dis.</i> 1999; 19(3): 271-85.	772	40.6	73
69	A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. <i>New Engl J Med.</i> 1995; 332(19): 1256-61.	771	33.5	90
70	Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. <i>Cell.</i> 2010; 140(2): 197-208.	768	96	28
71	Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, et al. Small hepatocellular carcinoma in cirrhosis: Randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. <i>Radiology.</i> 2003; 228(1): 235-40.	762	50.8	59
72	Reddy JK, Azarnoff DL, Hignite CE. Hypolipidaemic hepatic peroxisome proliferators form a novel class of chemical carcinogens. <i>Nature.</i> 1980; 283(5745): 397-8.	761	20	99
73	Ma S, Chan K, Hu L, Lee TK, Wo JY, Ng IO, et al. Identification and Characterization of Tumorigenic Liver Cancer Stem/Progenitor Cells. <i>Gastroenterology.</i> 2007; 132(7): 2542-56.	760	69.1	43
74	Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. <i>Lancet Oncol.</i> 2009; 10(1): 35-43.	749	83.2	34
75	Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. <i>Ann Surg.</i> 1993; 218(2): 145-51.	747	29.9	92
76	El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. <i>Ann Intern Med.</i> 2003; 139(10): 817-23.	746	49.7	62
77	Hoshida Y, Villanueva A, Kobayashi M, Peix J, Chiang DY, Camargo A, et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. <i>New Engl J Med.</i> 2008; 359(19): 1995-2004.	744	74.4	38
78	Colombo M, de Franchis R, Del Ninno E, Sangiovanni A, de Fazio C, Tommasini M, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. <i>New Engl J Med.</i> 1991; 325(10): 675-80.	742	27.5	93
79	El-Serag HB, Tran T, Everhart JE. Diabetes Increases the Risk of Chronic Liver Disease and Hepatocellular Carcinoma. <i>Gastroenterology.</i> 2004; 126(2): 460-8.	738	52.7	57
80	Satoh S, Daigo Y, Furukawa Y, Kato T, Miwa N, Nishiwaki T, et al. AXIN1 mutations in hepatocellular carcinomas, and growth suppression in cancer cells by virus-mediated transfer of AXIN1. <i>Nat Genet.</i> 2000; 24(3): 245-50.	725	40.3	74
81	Yang ZF, Ho DW, Ng MN, Lau CK, Yu WC, Ngai P, et al. Significance of CD90+ Cancer Stem Cells in Human Liver Cancer. <i>Cancer Cell.</i> 2008; 13(2): 153-66.	724	72.4	39
82	Llovet JM, Bustamante J, Castells A, Vilana R, Del Carmen Avuso M, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: Rationale for the design and evaluation of therapeutic trials. <i>Hepatology.</i> 1999; 29(1): 62-7.	723	38.1	78
83	Copur MS. Sorafenib in advanced hepatocellular carcinoma [3]. <i>New Engl J Med.</i> 2008; 359(23): 2498.	721	72.1	40
84	Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the PRECISION v study. <i>Cardiovasc Intervent Radiol.</i> 2010; 33(1): 41-52.	720	90	32
85	Llovet JM, Bruix J. Molecular targeted therapies in hepatocellular carcinoma. <i>Hepatology.</i> 2008; 48(4): 1312-27.	718	71.8	41
86	Maeda S, Kamata H, Luo JL, Leffert H, Karin M. IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. <i>Cell.</i> 2005; 121(7): 977-90.	713	54.8	56
87	Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. <i>J Cancer Res ClinOncol.</i> 2004; 130(7): 417-22.	711	50.8	60
88	Zender L, Spector MS, Xue W, Flemming P, Cordon-Cardo C, Silke J, et al. Identification and Validation of Oncogenes in Liver Cancer Using an Integrative Oncogenomic Approach. <i>Cell.</i> 2006; 125(7): 1253-67.	696	58	53
89	Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: A weighty connection. <i>Hepatology.</i> 2010; 51(5): 1820-32.	684	85.5	33
90	Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. <i>Ann Surg.</i> 1999; 229(6): 790-800.	671	35.3	87
91	Jonas S, Bechstein WO, Steinmüller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. <i>Hepatology.</i> 2001; 33(5): 1080-6.	667	39.2	77
92	Curley SA, Izzo F, Ellis LM, Vauthey JN, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. <i>Ann Surg.</i> 2000; 232(3): 381-91.	659	36.6	83
93	Ikeda K, Saitoh S, Koida I, Arase Y, Tsubota A, Chayama K, et al. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. <i>Hepatology.</i> 1993; 18(1): 47-53.	654	26.2	95
94	Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. <i>J Hepatol.</i> 2003; 38(2): 200-7.	650	43.3	70
95	Bruix J, Barrera JM, Calvet X, Ercilla G, Costa J, Sanchez-Tapias JM, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. <i>Lancet.</i> 1989; 2(8670): 1004-6.	646	22.3	98
96	Lustig B, Jerchow B, Sachs M, Weiler S, Pietsch T, Karsten U, et al. Negative feedback loop of Wnt signaling through upregulation of conductin/ axin2 in colorectal and liver tumors. <i>Mol Cell Biol.</i> 2002; 22(4): 1184-93.	639	39.9	75
97	Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. <i>Lancet.</i> 2000; 356(9232): 802-7.	636	35.3	86
98	Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, 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? <i>Hepatology.</i> 2008; 47(1): 82-9.	634	63.4	50
99	Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. <i>J Hepatol.</i> 2008; 48 Suppl 1: S20-37.	631	78.9	35
100	Nishiwaki-Matsushima R, Ohta T, Nishiwaki S, Suganuma M, Kohyama K, Ishikawa T, et al. Liver tumor promotion by the cyanobacterial cyclic peptide toxin microcystin-LR. <i>J Cancer Res ClinOncol.</i> 1992; 118(6): 420-4.	618	23.8	96

Table 2 Authors with ≥ 5 articles in the top 100 articles.

Author	Total articles	Authorship position			Author affiliations	H-index
		First	Last	Other		
Bruix, J.	19	5	10	4	Universitat de Barcelona, Barcelona Clinic Liver Cancer (BCLC) Group, Barcelona, Spain	80
Llovet, J.M.	17	10	2	5	Icahn School of Medicine at Mount Sinai, Department of Medicine, New York, United States	95
El-Serag, H.B.	7	7	0	0	Baylor College of Medicine, Department of Medicine, Houston, United States	92
Lencioni, R.A.	6	2	1	3	University of Miami Leonard M. Miller School of Medicine, Department of Vascular and Interventional Radiology, Miami, United States	60
Livraghi, T.	5	5	0	0	Istituto Clinico Humanitas, Rozzano, Italy	49
Mazzaferro, V.	5	2	0	3	Universita degli Studi di Milano, Gastrointestinal Surgery and Liver Transplantation, Milan, Italy	60

Table 3 Top-cited articles according to journal and their impact factors (only journals with >2 articles have been shown).

Journal Name	Number of articles	Impact factor 2017
Hepatology	15	13.2
New England Journal of Medicine	11	72.4
Gastroenterology	9	18.4
Nature	7	40.1
The Lancet	7	47.8
Annals of Surgery	6	8.98
Journal of Hepatology	5	12.5
Radiology	5	7.3
Cell	4	30.4
Cancer	3	5.99
Seminars in Liver Disease	3	5.5

A number of institutions contributed to the top 100 articles. University of Barcelona contributed the greatest number of articles ($n = 13$), followed by Baylor College of Medicine ($n = 6$). Based on first author institutional affiliations, institutions which contributed more than 2 articles in our list are shown in Table 4.

4. Type of Article and Topical Distribution

We divided the top 100 cited articles into 3 categories, according to the type of study: original articles ($n = 75$), review/expert opinion ($n = 20$) and official guidelines ($n = 5$). Figure 3 shows the temporal trend of publication by type of article. Original articles were further subdivided according to article’s main focus into 5 categories: genetics and pathophysiology ($n = 27$), management ($n = 24$), epidemiology/natural history ($n = 19$), prognostication ($n = 3$) and surveillance ($n = 2$).

Of the top 40 most cited articles, 35% ($n = 14$) were focused on management, while this figure rose to 70% ($n = 7$) among the top 10 articles. This pattern is also reflected in the citations-per-year ranking, indicating that the exceptionally high citation counts of management articles are not attributable to earlier publication.

DISCUSSION

Research Activity and Trends

As shown in Figures 1 and 3, the time period from 1991 to 2010 saw the publication of a large majority of the 100 most-cited articles in the list ($n = 82$); furthermore, the distribution of these articles through this period reflects an exponential increase in research activity. This pattern of literature growth has been identified by a variety of bibliometric analyses in the past-notably, by studies analyzing the literature on clinically relevant topics such as diabetes^[5] or chikungunya^[13], which suggests the modern significance of HCC as a disease entity to be dealt with in clinical practice. Additionally, as suggested by previous studies,^[14] the increasing number of publications since 1991 may be also be linked to the establishment of the World Wide Web. Fur-

Table 4 Institutions that contributed ≥ 2 articles in the top 100 cited list.

Institute, country	Number of articles
University of Barcelona, Spain	13
Baylor College of Medicine, United States	6
Ospedale Civile, Italy	5
Institut Catala d'Oncologia, Spain	2
Mount Sinai School of Medicine, United States	2
National Cancer Institute, Italy	2
University of Pisa, Italy	2
University of Texas M.D. Anderson Cancer Center, United States	2
University of Washington Medical Research Unit, Taiwan	2

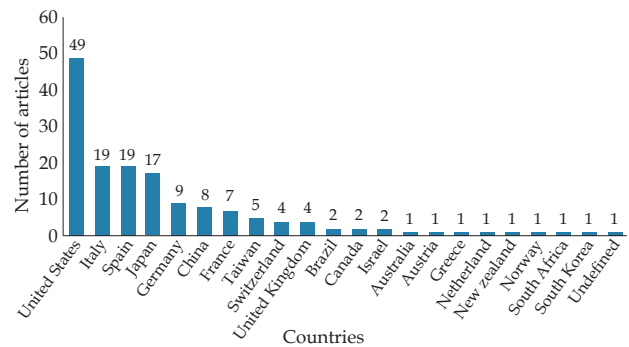


Figure 2 Number of articles originating from each country.

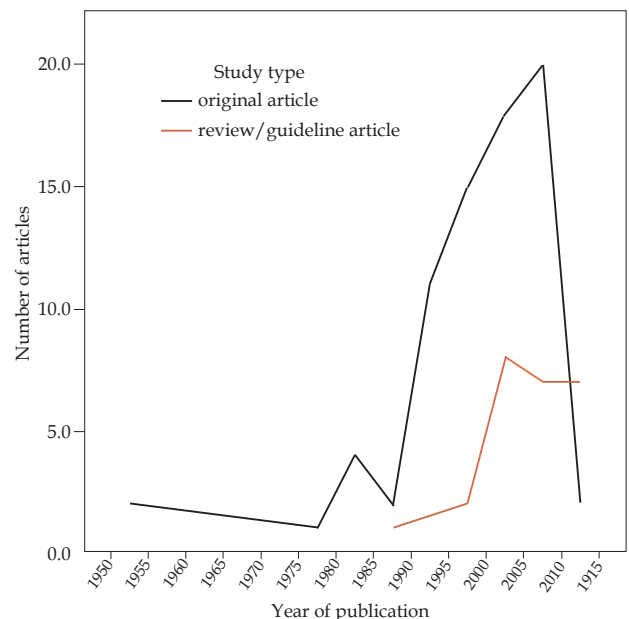


Figure 3 The number of articles published over 5-year intervals, by study type.

ther analysis of the articles published in this interval pinpoints peak research activity to be in the period from 2006 to 2010. The specific subject matter of these articles provides valuable insight into potential breakthroughs in the field — most importantly, the emergence of sorafenib as a novel therapeutic agent for HCC.

During the 2006-2010 periods alone, 5 articles (out of the 29 published during these years) were seen to explore the therapeutic potential of sorafenib. Collectively, these randomized controlled trials (RCTs) and experimental studies served to highlight the significant survival benefit and acceptable tolerance to sorafenib, which may be responsible for a shift in treatment strategies. While sorafenib-based studies were found to predominate in the 2006-2010 period, the majority of articles focusing on liver transplantation or resection were published from 1993 to 2001, whereas articles exploring chemoembolization and radiofrequency ablation for unresectable tumors were published mainly from 1995 to 2003. Overall, this signifies a growing interest in applying targeted therapeutics to the field of HCC.

Additionally, analysis of the top-cited articles also shows a sudden decline in research activity from 2011 to 2015 after the exponential increase. This may simply be attributed to the temporal disadvantage of newer articles, given that they have had little time to garner citations. The introduction of a ranking by citations-per-year (Table 1) reduces this bias considerably and emphasizes the significance of recently-published articles higher up in this ranking. On the other hand, the past 5-6 years have also seen the publication and frequent updating of reviews and clinical guidelines in favor of original articles.

Content

Survey of the findings and rationale of the top 10 most-cited articles allows clear identification of the gaps in literature bridged by these studies, and puts their contribution to the field of HCC into perspective. Excluding clinical guidelines, 2 of the top 10 most-cited articles provide clinical evidence of the therapeutic benefit of sorafenib in advanced HCC, while another study highlights liver transplantation as an effective treatment. Apart from clinical studies, 3 of the highest-cited articles review the epidemiological aspects of HCC; proposing strategies for prevention and prognostication in view of known risk factors, defining molecular pathways, and underlining the shifting incidence of HCC from older to younger patient populations over time. Among pathophysiology-based articles, the relationship between HCC incidence and hepatitis B or C seems to be of particular interest, as well as the role of genetic alterations such as *p53* mutations. More importantly, the increasing number of citations garnered by management-based articles in recent years may align with attempts being made towards the development and assessment of curative procedures for HCC. Although the initial percentage of articles discussing management in the top 100 list is 24%, this increases to 35% in the top 40 most-cited articles and 70% in the top 10 most-cited articles. This pattern is also reflected in the citations-per-year ranking, indicating that the exceptionally high citation counts of management articles are not attributable to earlier publication. In comparison with bibliometric analyses of other hepatic pathologies, the literature exploring Budd-Chiari syndrome shows a similar focus on clinical reports^[15], while studies on non-alcoholic fatty liver disease favor pathogenesis and epidemiology^[16].

Journals

Table 3 summarizes the journals that most frequently contained the top-cited articles, along with their respective impact factors. The highest numbers of articles were found to be published in the specialty journal *Hepatology*. Overall, however, our analysis shows a

fairly even distribution of articles to general versus specialty journals (52% vs. 48% respectively). Moreover, the broad readership and high impact factors of journals such as *New England Journal of Medicine*, *The Lancet* and *Nature* indicate the importance of these studies and their results to the scientific community as a whole. Such high-impact journals (impact factor ≥ 30) represent 35% of all publications in the list, while the median impact factor for journals in our list was 15.2. This figure is higher than that reported for citation classics in other fields such as gastric cancer^[8] (median impact factor 9.28), reinforcing the relative impact of HCC in academic research.

Unlike several fields such as cardiovascular^[7], diabetes^[5] and thrombolytics^[17] research, our analysis did not identify a correlation between journal impact factor and the number of top-cited articles published in that journal. This may be related to the near-equal contribution of specialty journals among the top 100 cited articles, as these journals tend to have narrower readership- indicating the need for and importance of sub-specialized expertise in the field of HCC.

Origins and Authors

As denoted in Figure 2, USA has contributed the highest number of top-cited articles to HCC literature by a large margin, followed by Western European countries. These findings are unsurprising, given the number of established research institutes in the US and the widespread availability of resources. Furthermore, 31% of articles were found to be multi-origin, thus implying open exchange of information across borders and solidifying the role of such international exchange in producing high-quality research. Apart from this, the overwhelming disease burden of HCC in sub-Saharan Africa and Eastern Asia^[18] strongly encourages a global effort to increase the productivity of these countries so as to evaluate these populations more thoroughly.

In terms of authorship, it is interesting to note that the author and institute with the highest number of publications originate from Spain, rather than USA. The recognition of individual authors helps to identify significant influences in the field of research and potentially cements the increased value of their work. However, only 6 authors were found to contribute more than 5 articles to the top 100 list, which may indicate a lack of prominent thought leaders despite the high overall productivity of the field.

Limitations

As a citation classic, this analysis is subject to various types of bias that may interfere with accurate representation by citation count. This includes institutional bias, language bias, powerful person bias, and in-house bias^[19]. We calculated self-citations among the total number of citations, and found them to be around 3%, indicating that bias resulting from self-citations is minimal in our analysis. Furthermore, we utilized only one database in our study to collect references, which may have resulted in the omission of articles not recognized by Scopus. Finally, despite the production of a separate list by citations-per-year, high-quality articles published in 2015 or later require a certain number of years to garner citation counts reflecting their impact, due to which any such recent articles would likely be excluded from our list.

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