

Hepatocellular carcinoma's 100 most influential manuscripts: A bibliometric analysis

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ABSTRACT

Aims: A bibliometric analysis identifies the major publications that influence the clinical management of Hepatocellular Carcinoma (HCC). Within this study, the 100 most cited HCC articles are noted and analysed. **Methods:** The search terminology "Hepatocellular carcinoma" and "HCC" were used to search through the Thomson Reuters Web of Science database. The inclusion criteria consisted of English language full articles. The subject matter, author and institution details, year of publication and journal were recorded for the 100 most cited HCC articles. Citation rate index was calculated by dividing the number of citations by the number of years since publication. **Results:** The search through the Thomson Reuters Web of Science database identified 39,518 eligible papers. The median (range) citation number was 909 (4419 to 458). The most cited article (produced by Llovet et al) discussed the role of Sorafenib in advanced HCC (4419 citations). Hepatology published the most articles (n=20, 20,533 citations), however the Lancet had the overall highest citation number of 39219, across 9

published articles. The most discussed topic was HCC management (n=31), followed by prognosis (n=18) and aetiology (n=15). **Conclusion:** This bibliometric analysis has identified the 100 most cited HCC articles. Through integrating new knowledge into clinical practice, this has enabled novel treatment strategies to be utilised for patients with HCC. This study highlights what makes a citable article and may aid in the development for future HCC research themes.

Keywords: Bibliometric analysis, Hepatocellular carcinoma, Management

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INTRODUCTION

Within current clinical practice, the most common primary liver malignancy is Hepatocellular carcinoma (HCC) [1]. A combination of intrinsic factors (aberrant epigenetic alterations) and extrinsic risk factors, produces dysregulated cell signaling pathways that result in tumorigenesis within the primary liver parenchyma cell lines, the hepatocytes [2]. The global incidence of HCC is increasing [3]. A SEER-Medicare database review highlighted the significant socio-economic burden of HCC on today's society [4]. In light of the disease's prevalence and clinical outcomes, research has been focused on

enhancing our understanding of the pathophysiology of the disease and developing novel treatment strategies. Increasing our understanding of HCC will govern and influence current clinical practice, thus ensuring that appropriate management algorithms are created and surveillance screening protocols can be implemented for high-risk patient cohorts.

One method of identifying published research of the most intellectual influence is through creating a citation rank list [5]. After a manuscript is published, if it is referenced by another peer-reviewed article, a citation is generated. It is proposed that original research with the greatest influence would subsequently be cited several times. Citation analysis enables the ranking of published research based upon the total number of citations each individual article has received. This method can be implemented to create a list of journals that have had a significant impact on their respected specialty [5].

Several surgical specialties have performed a citation rank analysis in an attempt to identify the most influential papers from within their own respective field [6–8]. No study has assessed for the most influential HCC manuscripts. Such an analysis would facilitate our understanding of how our knowledge of HCC has developed and subsequently impacted on clinical management. The aim of this study is to identify the studies of greatest clinical influence that has augmented our knowledge regarding HCC.

MATERIALS AND METHODS

A search through the online Thomson Reuters Web of Science citation indexing database was performed. Predefined search terminologies were incorporated into the search. The search strategy included “hepatocellular carcinoma” and “HCC”. Boolean operators were included in order to optimise the accuracy of the search and to facilitate large data capture. Two independent researchers conducted the search simultaneously in order to ensure that the search was accurate and that all relevant manuscripts were identified and included. The search result from the Thomson Reuters Web of Science database was subsequently filtered to include full manuscripts of English language only. The results were further sorted by number of citations as described previously. The exclusion criteria for this study included all non-English manuscripts and manuscripts that did not specifically focus on HCC related research. The 100 most cited HCC related articles were identified and documented. Each article was reviewed and data was obtained for the following variables: topic, author list, year of publication, country of origin and publishing journal. Every included journal had its individual and five year impact factor recorded. Due to the nature and methodology used for bibliometric analyses, this type of study is susceptible to bias. One such limitation is that historical manuscripts may accrue a higher number of

citations over time despite missing the influence of newer ‘higher impact’ publications. In an attempt to overcome such a limitation, the citation rate index was calculated by dividing the number of citations by the number of years since publication.

RESULTS

A total of 39,518 full length, English language papers were identified following a search through the Thomson Reuters Web of Science database. Table 1 illustrates the 100 most cited HCC articles [9–108]. A wide range of citations was noted, ranging from 4419 by Llovet et al. (Sorafenib in advanced hepatocellular carcinoma) to 458 by Llovet et al. (Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma) [9, 108]. Guichard et al. in 2012 published the latest manuscript (Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma) [103]. Whereas, the oldest published manuscript was published in 1989 by Colombo et al. (Prevalence of Antibodies to Hepatitis-C virus in Italian patients with Hepatocellular-carcinoma) [68].

The articles were published across 21 journals (Table 2). The range of articles published per journal was 1–20. Hepatology published the most articles (n=20), resulting in a total citation rate of 20,533. The Lancet had the overall highest citation rate of 39,219, despite only publishing 9 articles. The journal with the highest impact factor and five-year impact factor was the New England Journal of Medicine (72.406 and 64.201 respectively).

A wide geographical distribution of the articles within the 100 most cited HCC articles was noted (Figure 1). The United States of America was the country that produced the highest number of papers that featured within the 100 most cited HCC manuscripts (n=32), followed by Japan (n=19) and Spain and Italy (n=13, respectively). The University of Tokyo (Japan) had the greatest number of published manuscripts (n= 8) followed by Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) institute (Spain) (n=7) (Table 3). Two authors (Bruix J, Llovet J) had 6 first author publications within the 100 most cited articles and one author had five first name publications (Livraghi, T).

The citation rate index is defined in the literature through a specific formula; the number of citations an article has received divided by the number of years since its original publication [8, 109] (Table 4). The citation rate index was calculated for all articles, the highest citation rate index for the top 10 articles ranged from 498 by Bruix, et al. (Management of Hepatocellular Carcinoma: An Update) to 142 by Chen, et al. (Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level) [12, 20].

Each manuscript was reviewed in order to identify its principle subject matter (Table 5). Of the 100 most

Table 1: The 100 most cited HCC articles

Rank	Citations	First author	Rank	Citations	First author
1	4419	Llovet, J [9]	51	672	Chen, M [59]
2	3,497	Mazzaferro, V [10]	52	645	Ikeda, K [60]
3	3,408	Bruix, J [11]	53	642	Shafritz, D [61]
4	2,985	Bruix, J [12]	54	639	Hoshida, Y [62]
5	2703	Bruix, J [13]	55	636	Wang, J [63]
6	2695	Llovet, J [14]	56	634	CLIP Investigators [64]
7	2093	Beasley, R [15]	57	633	Lencioni, R [65]
8	2037	El-Serag, H [16]	58	625	El-Serag, H [66]
9	1,914	Cheng, A [17]	59	613	El-Serag, H [67]
10	1776	Knowles, B [18]	60	608	Colombo, M [68]
11	1703	Llovet, J [19]	61	605	Benbrook, D [69]
12	1565	Chen, C [20]	62	598	Llovet, J [70]
13	1506	Meng, F [21]	63	588	Fong, Y [71]
14	1469	Forner, A [22]	64	573	Jonas, S [72]
15	1,412	Okuda, K [23]	65	571	Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire [73]
16	1,352	Hsu, I [24]	66	565	El-Serag, H [74]
17	1307	Bosch, F [25]	67	561	Imamura, H [75]
18	1169	Bressac, B [26]	68	554	Chisari, F [76]
19	1133	Lo, C [27]	69	549	Curley, S [77]
20	1084	Chang, M [28]	70	546	Zhang, B [78]
21	1056	Kiyosawa, K [29]	71	544	Lammer, J [79]
22	1053	Yao, F [30]	72	538	Takayama, T [80]
23	1023	Saito, I [31]	73	530	Nakayama, J [81]
24	1013	Llovet, J [32]	74	530	Lee, J [82]
25	984	Kota, J [33]	75	529	Muto, Y [83]
26	962	Thorgeirsson, G [34]	76	528	Gramantieri, L [84]
27	941	Fattovich, G [35]	77	520	Livraghi, T [85]
28	924	Beasley, R [36]	78	514	Ye, Q [86]
29	912	Livraghi, T [37]	79	513	Arii, S [87]
30	900	Kim, C [38]	80	512	Brechot, C [88]
31	855	Moriya, K [39]	81	506	Yamashita, T [89]
32	844	Tsukuma, H [40]	82	504	Fan, S [90]
33	835	Bugianesi, E [41]	83	500	Yoshikawa, H [91]
34	788	Altekruse, S [42]	84	499	Shiina, S [92]
35	758	Abou-Alfa, G [43]	85	497	Gao, Q [93]
36	747	Yoshida, H [44]	86	496	Belghiti, J [94]
37	745	de La Coste, A [45]	87	485	Tateishi, R [95]
38	745	Nishiguchi, S [46]	88	480	Poon, R [96]
39	740	Yang, H [47]	89	476	Iwatsuki, S [97]
40	740	Livraghi, T [48]	90	476	Camma, C [98]
41	733	Satoh, S [49]	91	472	Ross, R [99]
42	719	Murakami, Y [50]	92	472	Shachaf, C [100]
43	716	Livraghi, T [51]	93	468	Bruix, J [101]
44	713	Liu, L [52]	94	468	Lee, J [102]
45	704	Livraghi, T [53]	95	466	Guichard, C [103]
46	700	Bismuth, H [54]	96	464	Omata, M [104]
47	697	Colombo, M [55]	97	464	Lencioni, R [105]
48	691	Bruix, J [56]	98	463	Boyault, S [106]
49	685	Bruix, J [57]	99	459	Nakashima, T [107]
50	674	Wanless, I [58]	100	458	Llovet, J [108]

Table 2: Journals with the top 100 cited HCC articles

Journal Title	Impact factor as of 2017	5 year impact factor	Number of manuscripts in the top 100	Number of citations
Hepatology	13.246	11.93	20	20,533
New England Journal of Medicine	72.406	64.201	11	15680
Annals of Surgery	8.98	9.41	9	5011
Gastroenterology	18.392	16.825	9	7227
Lancet	47.831	48.082	9	36,213
Radiology	7.296	7.648	8	5082
Nature	40.137	43.769	7	5,627
Cancer	5.238	5.517	4	1862
Nature genetics	27.959	31.694	4	2710
Journal of Clinical Oncology	24.008	19.311	3	2042
Nature medicine	29.886	32.261	3	1897
Cancer research journal	9.122	9.826	2	1224
Cell	30.41	34.103	2	1533
Proceedings of the National Academy of Sciences of the United States of America	9.661	10.414	2	1768
Annals of Internal Medicine	17.135	17.609	1	747
CardioVascular and Interventional Radiology	2.191	2.15	1	538
Journal of Cancer Research and Clinical Oncology	3.503	3.144	1	544
Journal of the American Medical Association	44.405	38.209	1	1565
Lancet Oncology	33.9	31.194	1	1914
Oncogene	7.519	7.272	1	716
Science	37.205	38.062	1	1776

Table 3: Institutions with the highest numbers of papers in the top 100

Name of institution	Number of Publications in top 100	Total number of citations
University of Tokyo	8	4846
Institut d'Investigacions Biomèdiques August Pi i Sunyer	7	14861
Hospital Clínic i Provincial	5	3983
National Cancer Institute	3	2254
Ospedale Civile	3	2126
Harvard University	2	1349
Fudan University	2	1040
National Taiwan University	2	2305
University of Hong Kong	2	1609
Ohio State University	2	2490
Memorial Sloan Kettering Cancer Center	2	1331
Michael E. DeBakey VA Medical Center	2	1174

Table 4: The top 10 highest citation rate index HCC articles

Rank	Citation rate	First Author	Senior Author	Title	Institution	Country
1	498	Bruix, J [12]	Sherman, M	Management of Hepatocellular Carcinoma: An Update	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Spain
2	442	Llovet, J [9]	Bruix, J	Sorafenib in advanced hepatocellular carcinoma	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Spain
3	294	Forner, A [22]	Bruix, J	Hepatocellular carcinoma	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Spain
4	284	Bruix, J [11]	Sherman, M	Management of hepatocellular carcinoma	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Spain
5	239	Cheng, A [17]	Guan, Z	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	National Taiwan University Hospital	Taiwan
6	192	Llovet, J [14]	Bruix, J	Hepatocellular carcinoma	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Spain
7	169	Bruix, J [13]	Rodes, J	Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL Conference	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Spain
8	167	Mazzaferro, V [10]	Gennari, L	Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis	Department of Surgery	Italy
9	151	Meng, F [21]	Patel, T	MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer	Department of Internal Medicine	USA
10	142	Chen, C [20]	Iloeje, U	Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level	Graduate Institute of Epidemiology	Taiwan

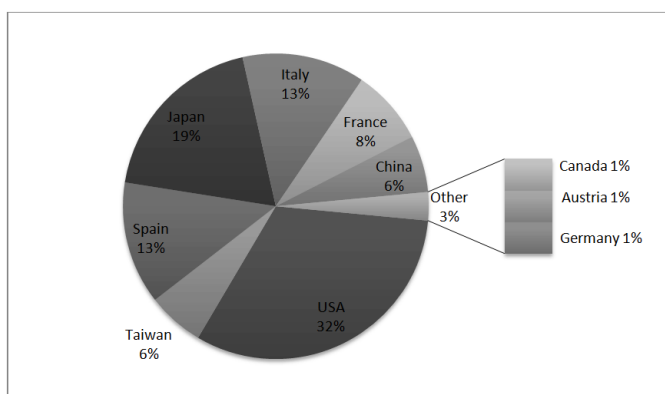


Figure 1: Geographical distribution of the 100 most cited HCC articles.

Table 5: Most referenced topics within the 100 most cited HCC articles *

Subject of paper	Number of papers
Management	31
Pathology	7
Aetiology	15
Epidemiology	10
Science	12
Prognosis	18
Genetics	12
Diagnosis	3
Pathophysiology	4
Histology	2

*Numerous manuscripts covered multiple topics, therefore the cumulative total does not add up to 100

cited HCC articles, management (31 articles) was the most frequently discussed topic followed by prognosis (n=15) and aetiology (n=15). Of management related articles, 11 discussed ablation as a HCC treatment strategy and 6 discussed surgical resection of HCC as a definitive and curative management strategy. Articles published prior to 1999 reported the following topics: aetiology of HCC, prognosis of the disease and epidemiological trends of HCC. Whereas articles published post 2000, mostly discussed management strategies for HCC.

DISCUSSION

Advances and expansion of novel treatment strategies (ranging from transplantation to ablation), the creation of prognostication systems and a further understanding on the impact of genetics on disease pathophysiology and aetiological risk factors represent 76% of the manuscripts within the 100 most cited HCC articles. This acquired knowledge influences current clinical practice and leads evidence based medicine. Identification of risk factors (notably the hepatitis viruses) has permitted the creation of surveillance and screening protocols for high-risk patient cohorts.

This bibliometric analysis included a range of different topics. Management of HCC was the main emphasis of 31 of the 100 most cited articles. Several different treatment strategies have been described for HCC. Surgical resection of HCC has historically been described as the main curative treatment option [87]. However, manuscripts evaluating the surgical management of HCC only accounted for 6 articles, thus underrepresented in this bibliometric analysis. Not all patients with HCC are candidates for surgical intervention. This may be due to tumor factors (large volume disease, bi-lobar disease, vascular involvement or inadequate liver remnant), patient factors (pre-existing comorbidities) or compromised liver function (secondary to liver cirrhosis) [110]. Historically, these patients were offered palliative treatment alone, however newer management strategies, such as radiofrequency ablation (RFA) can be used as a treatment options for this cohort of patients where surgery is contraindicated. It is not surprising that ablation was the most commonly described treatment strategy in this bibliometric analysis (11 articles). Both RFA and Microwave ablation (MWA) have been described within this bibliometric analysis. For patients with HCC and significant cirrhosis, pharmaceutical drug based manipulation is a key aspect of palliative therapy [111, 112], in particular the tyrosine kinase inhibitor, Sorafenib [43]. For any scientific researcher or clinician treating cancer, the clinical emphasis is achieving a cure whenever possible. The harsh reality is that this is not always possible, thus reinforcing the need to develop adjuvant treatments and palliative management strategies. As with other Upper Gastrointestinal cancers, notably

Oesophageal and Gastric cancer, the five year survival is poor. Bibliometric analyses reviewing Oesophageal and Gastric cancer have also highlighted that chemotherapy (in the context of neo/adjuvant or palliative chemotherapy) is frequently discussed topic in the 100 most cited articles (n=34 and n=10 respectively) [8, 113]. This demonstrates the importance of multimodal therapeutic approaches to treating cancer.

Our understanding of the natural history of HCC has significantly increased over the last decade. The identification of risk factors for HCC allows further risk stratification of patients. HCC aetiology represented 15 articles of the 100 most cited manuscripts. Historical risk factors for HCC development include chronic hepatitis, cirrhosis and Aflatoxin exposure [114]. However, with global rates of obesity rising, incidence rates of HCC are increasing as a consequence to the metabolic syndrome and subsequent non alcoholic steato-hepatitis (NASH) [114] 7. A bibliometric analysis is a dynamic and fluid process; over time newly acquired information will be integrated and dispersed throughout the subject field with reflexive changes in the 100 most cited articles. An argument could be made that a bibliometric analysis will need to be repeated every 5-10 years to identify avenues of important scientific traction. In the context of aetiology of HCC, it is hypothesized that repeating this bibliometric analysis in a decade would reflect NASH as a common causative mechanism which will likely have a greater representation in the 100 manuscripts [115].

Published manuscripts that significantly impact clinical practice are frequently read, analysed and subsequently cited. The total number of citations forms the basis of the impact factor. The most influential journals can be identified by using the impact factor (IF). The IF is defined as the average number of citations a published manuscript within a journal receives, in a specific time period. Within this bibliometric analysis, the journals with the highest IF were the New England Journal of Medicine (IF of 72.41), the Lancet (IF of 47.83) and the Journal of the American Medical Association (IF of 44.41). The median IF for this bibliometric analysis was 18.39. This is significantly higher than the median IF seen in bibliometric analyses on gastric and oesophageal cancer (9.28 and 15.69 respectively) [8, 115]. Possible reasons for this include the global burden of HCC on healthcare systems and the novelty of the manuscripts findings, representing break through in research within their respective field of specialization. Due to the geographical distribution and global prevalence of HCC, it is likely that key ground breaking concepts in both diagnosis and management of the disease are more likely to be accepted in high IF journals in order to obtain a wider audience and to have a greater impact on clinical practice. Journals with a very high IF (IF > 30) included 32% of all published manuscripts within this bibliometric analysis. Only 2 articles were published in journals with an IF less than 5.

There are inherent limitations associated with bibliometric studies of this kind. These include institutional bias, powerful person bias and English language bias. Due to the geographical distribution of HCC (Sub-Saharan Africa and South East Asia), there is an argument that large studies originated from these countries may have published within their own language, thus may not appear in our findings. However, it is likely that studies with significant findings would have been submitted to English language journals in order to achieve maximum global exposure and publicity. Another limitation of this study is the bibliometric analysis of first and last authors only. Moreover, only the institution of the first author was noted. It is likely that authors will have contributed to other highly cited studies, and this method of author analysis may underestimate the author contribution in general. Historical manuscripts accrue citations over time, however the calculation and use of the citation rate index addresses this limitation.

CONCLUSION

This bibliometric analysis identified the 100 most cited HCC manuscripts within the current literature. The two most cited topics within this bibliometric analysis were aetiological risk factors and therapeutic treatment options for HCC. The management algorithm for patients with HCC has significantly changed over the last decade. Treatment strategies are now available for a cohort of patients who were once considered palliative. This advancement reflects a greater understanding of HCC disease biology and has impacted on patient care. Over a third of the articles in this bibliometric analysis were published in very high impact factor journals (Impact factor > 30), thus representing the novelty and the global importance of their findings. The study serves as a reference point for potential future HCC research themes.

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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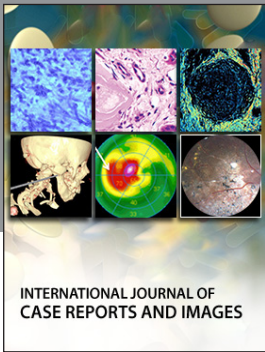
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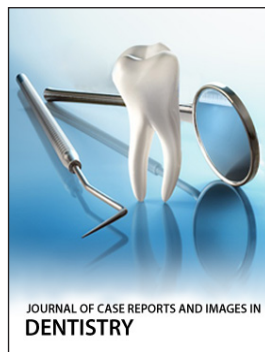
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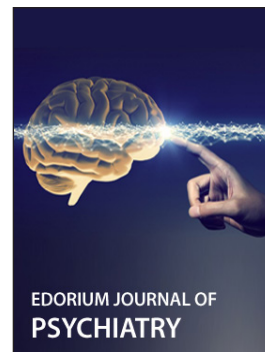
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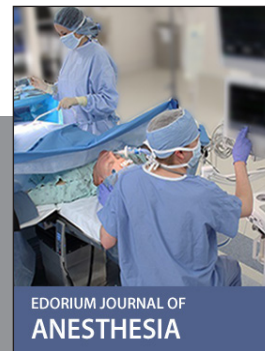
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