Trends in hepatocellular carcinoma research from 2008 to 2017: a bibliometric analysis

Yan Miao, Ying Zhang and Lihong Yin

Key Laboratory of Environmental Medicine Engineering of Ministry of Education, School of Public Health, Southeast University, Nanjing, China

ABSTRACT

Objectives. To comprehensively analyse the global scientific outputs of hepatocellular carcinoma (HCC) research.

Methods. Data of publications were downloaded from the Web of Science Core Collection. We used CiteSpace IV and Excel 2016 to analyse literature information, including journals, countries/regions, institutes, authors, citation reports and research frontiers.

Results. Until March 31, 2018, a total of 24,331 papers in HCC research were identified as published between 2008 and 2017. *Oncotarget* published the most papers. China contributed the most publications and the United States occupied leading positions in H-index value and the number of ESI top papers. Llovet JM owned the highest co-citations. The keyword "transarterial chemoembolization" ranked first in the research front-line.

Conclusions. The amount of papers published in HCC research has kept increasing since 2008. China showed vast progress in HCC research, but the United States was still the dominant country. Transarterial chemoembolization, epithelial-mesenchymal transition, and cancer stem cell were the latest research frontiers and should be paid more attention.

Subjects Gastroenterology and Hepatology, Oncology, Statistics

Keywords Hepatocellular carcinoma, Bibliometrics, CiteSpace IV, WoSCC

Submitted 1 June 2018
Accepted 30 July 2018
Published 15 August 2018

Corresponding author
Lihong Yin, 230169238@seu.edu.cn

Academic editor
Francis Boscoe

Additional Information and Declarations can be found on page 12

DOI **10.7717/peerj.5477**

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common type of primary liver malignancy and ranks third in the world's leading causes of cancer death (*Balogh et al., 2016*). The highest incidence rates of HCC worldwide are in East Asia and sub-Saharan Africa, with over 20 per 100,000 individuals (*Ghouri, Mian & Rowe, 2017*; *Zhu et al., 2016*). According to data from the Surveillance, Epidemiology, and End Results (SEER) program in the United States, HCC incidence remains relatively low compared to other primary cancers (*Mittal & El-Serag, 2013*). However, the incidence rate has risen nearly fivefold from 1.4 to 6.7 per 100,000 individuals over the past decades (*El-Serag & Kanwal, 2014*; *White et al., 2017*). Regarding gender, HCC prevalence worldwide in males is higher than in females. The sex ratio in HCC varies from 4:1 to 2:1, depending on geographical area (*Hefaiedh et al., 2013*; *Massarweh & El-Serag, 2017*). Due to its extensive prevalence, HCC

puts a substantial economic burden on the public health and medical system, whether in developed or developing countries.

Academic journals have published a large number of papers in HCC research since the past decade. However, no attempts have been made to analyse the data on publications systematically. Bibliometric analysis is defined as a quantitative analysis combining mathematical and statistical methods (*Pritchard, 1969*), and is a good choice for assessing trends in research activites (*Dalpé, 2002*). Moreover, bibliometric analysis focuses on the metrological characteristics of research literatures within a certain field (*Ellegaard & Wallin, 2015*), which helps investigators to grasp the development characteristics in this field over time and guide their follow-up work. In recent years, an increasing number of bibliometric studies have been published in high-impact medical journals (*Aggarwal et al., 2016*; *Almeida-Guerrero et al., 2018*; *Azer, 2015*; *Baek et al., 2018*; *Bruggmann et al., 2017*; *Khan et al., 2018*). Journals have also gradually shifted from publishing only conventional research to including bibliometric research (*Wakeling et al., 2017*).

The present study systematically evaluated HCC research from 2008 to 2017. We aimed to identify the mode of publications, construct research collaboration networks, and assess research trends and frontiers by time.

MATERIALS & METHODS

Data source and search strategy

Literature retrieval was done online through the Science Citation Index-Expanded (SCI-E) of the Web of Science Core Collection (WoSCC) on March 31, 2018. All searches were done within the same day, to avoid the bias caused by the daily database updates. The search terms were used as follows: = (“hepatocellular carcinoma*”) OR = (“hepatic cell carcinoma*”) OR = (“liver cell carcinoma*”) OR = (“liver carcinoma rupture”) OR = (“primary liver cancer*”) OR = (“primary liver carcinoma*”) OR = (“malignant hepatoma*”) OR = (“hepatocarcinoma*”) OR = (“hepatoma*”) AND Language= English. In the present study, only original and review papers were included.

Data collection

Raw data from WoSCC were initially downloaded and verified by two authors (YZ and YM) independently. The data were then imported into Excel 2016 (Redmond, WA, USA) and CiteSpace IV (Drexel University, Philadelphia, PA, USA), and systematically analysed. Any differences were unified by discussion.

Statistical methods

The WoSCC literature analysis report was used to analyse publication characteristics, including countries/regions, institutes, authors, journal sources, citation counts, number of annual publications, impact factor and H-index. The impact factor is an indicator that reflects the average number of yearly citations for recent papers published in the journal (*Garfield, 2006*). It is used to assess the quantity of research output in most bibliometric studies. H-index is a measure calculating both the productivity and citation impact per publication of a country, institute, scholar, and so forth (*Costas & Bordons, 2007*). It usually serves as an indicator for assessing the quality of scientific output.

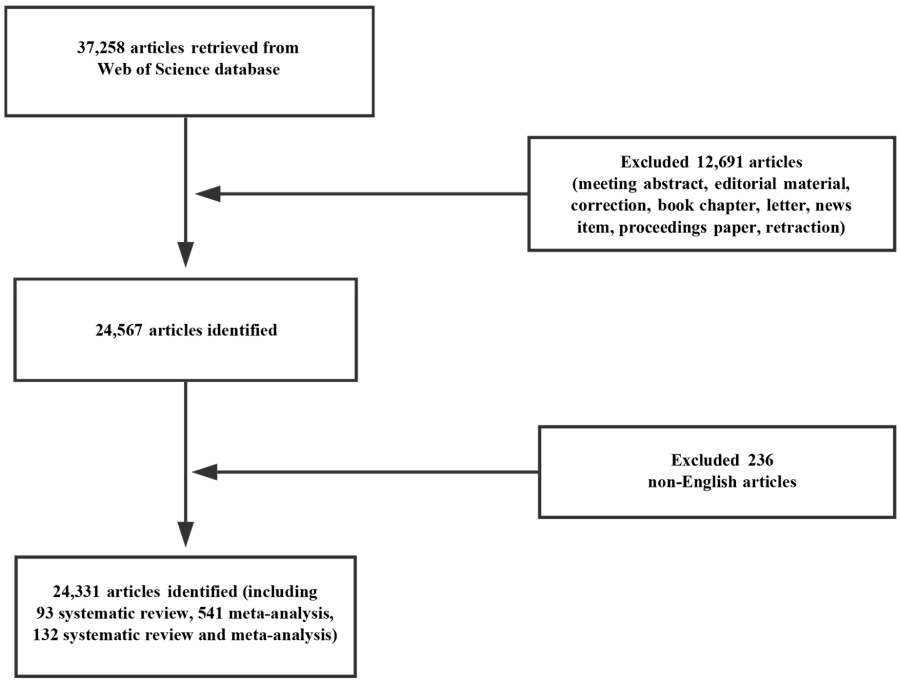

Figure 1 **Flow chart of hepatocellular carcinoma research inclusion.**
Full-size DOI: 10.7717/peerj.5477/fig-1

Excel 2016 was used to analyse the publication trend. The polynomial model $f(x) = ax^3 + bx^2 + cx + d$ was applied to forecast the growth of publications in the following year. Variable x stands for the publication year and $f(x)$ stands for the number of publications.

CiteSpace IV was used to analyse the association between journals, explore collaboration networks between authors/institutes/countries, identify co-cited authors/references, capture keywords with strong citation bursts, and construct visualization maps of all items mentioned above. In the present study, the individual network was derived from the 50 most highly cited papers in a one-year slice (*Chen, 2004*). Moreover, we used the TF-IDF weighting to analyse the contents of each cluster. TF-IDF, an abbreviation of term frequency-inverse document frequency, is a statistical algorithm reflecting how significant a word to a corpus of documents (*Ramos, 2003*).

RESULTS

Annual publications and growth forecast

In total, 24,331 papers (Fig. 1, Fig. S1) matched the retrieval criteria, including 93 systematic reviews, 541 meta-analysis, and 132 systematic review and meta-analysis. The number of publications by year was presented in Fig. 2A, where the overall trend consistently kept rising from 1,348 articles in 2008 to 3,572 articles in 2017.

The polynomial curve fitting of publication growth in HCC research showed a significant correlation (the coefficient of determination $(R^2) = 0.9985$) between publication year and

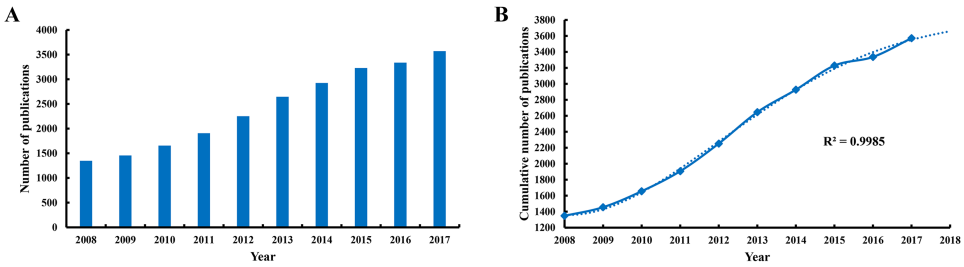

Figure 2 Publication outputs and growth forecast. (A) The annual number of publication in hepatocellular carcinoma research from 2008 to 2017. (B) The polynomial curve fitting of publication growth in hepatocellular carcinoma research.

Full-size DOI: 10.7717/peerj.5477/fig-2

Table 1 The top 15 journals that published articles in hepatocellular carcinoma research.

Rank	Journal title	Country	Count	Percent	IF 2016
1	Oncotarget	United States	852	3.50	5.168
2	PLOS One	United States	794	3.26	2.806
3	World Journal of Gastroenterology	United States	705	2.90	3.365
4	Hepatology	United States	500	2.06	13.246
5	Oncology Reports	Greece	423	1.74	2.662
6	Tumor Biology	England	413	1.70	3.650
7	Hepatology Research	Japan	365	1.50	2.602
8	Oncology Letters	Greece	351	1.44	1.390
9	Journal of Hepatology	Netherlands	327	1.34	12.486
10	Hepato-Gastroenterology	Germany	283	1.16	NA
11	Journal of Gastroenterology and Hepatology	Australia	279	1.15	3.452
12	Liver International	Denmark	265	1.09	4.116
13	Cancer Letters	Netherlands	259	1.06	6.375
14	Scientific Reports	England	259	1.06	4.259
15	BMC Cancer	England	244	1.00	3.288

number of publications (Fig. 2B). Through curve fitting, the number of publications was estimated to reach 3,660 in 2018.

Distribution of journals

In total, 1,681 academic journals (Dataset S1) have published papers in HCC research. Table 1 presented the top 15 journals contributing to HCC research. *Oncotarget* (impact factor (IF) 2016 = 5.168), published the most papers (852 publications, 3.50%), followed by *PLOS ONE* (IF 2016 = 2.806; 794 publications; 3.26%), *World Journal of Gastroenterology* (IF 2016 = 3.365; 705 publications; 2.90%), and *Hepatology* (IF 2016 = 13.246; 500 publications; 2.06%).

Figure 3 displayed the dual-map overlay of journals. The left and right sides corresponded to the citing and cited journals maps, respectively. The labels represented the disciplines covered by the journal. The lines on the map started from the left and ended on the right, representing the citation links. There were three main citation paths shown on the map.

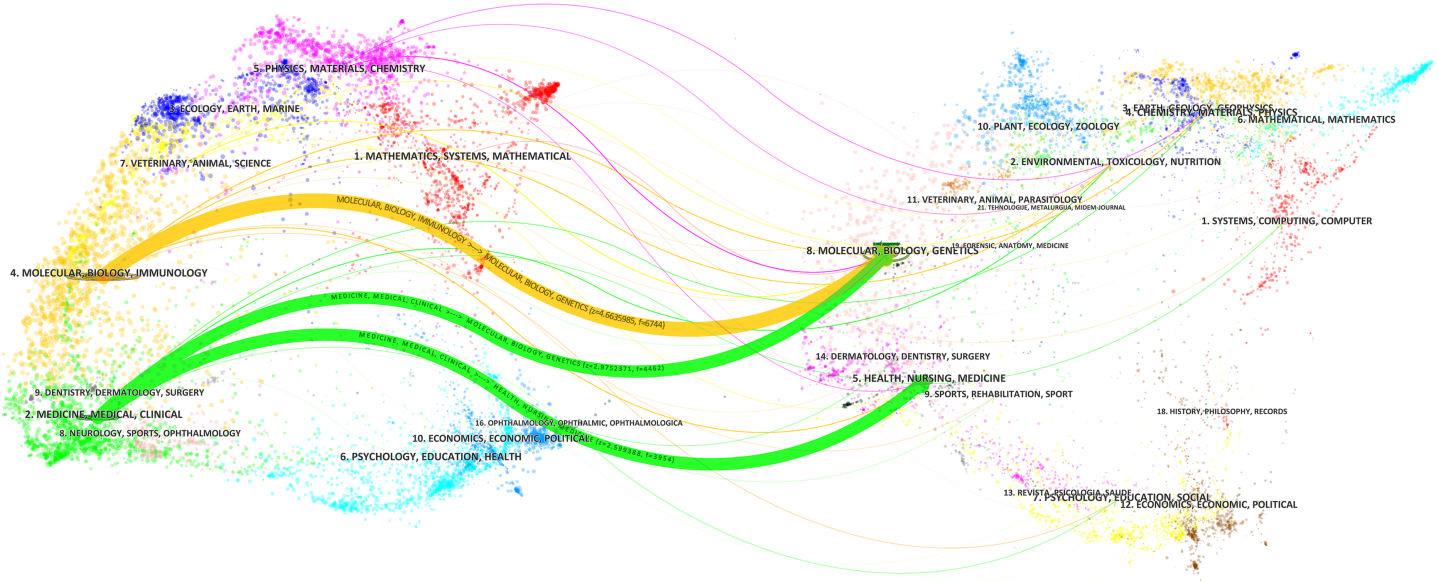

Figure 3 The dual-map overlay of journals related to hepatocellular carcinoma research. There were three citation paths. The yellow path, papers published in immunology/biology journals mostly cited journals in biology/genetics area; the middle green path, papers published in medical/clinical journals partially cited journals in biology/genetics area; the bottom green path, papers published in medical/clinical journals partially cited journals in health/medicine area.

Full-size DOI: 10.7717/peerj.5477/fig-3

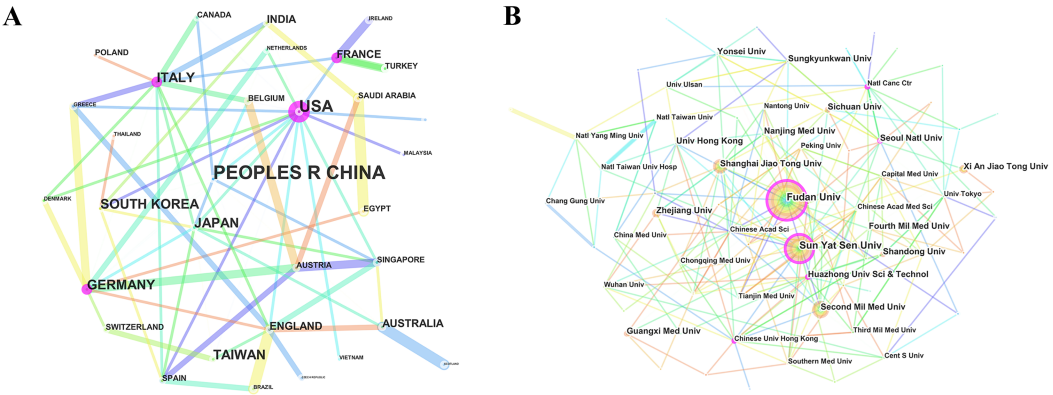

Figure 4 The distribution of countries and institutes. (A) The network map of countries/regions that involved in hepatocellular carcinoma research. (B) The network map of institutes that involved in hepatocellular carcinoma research.

Full-size DOI: 10.7717/peerj.5477/fig-4

Distribution of countries and institutes

The 24,331 papers in HCC research were contributed by 116 countries/regions (Dataset S2). Extensive collaborations were observed between countries/regions (Fig. 4A). According to the list of top 10 countries/regions (Table 2) engaged in HCC research, China contributed the most publications (10,755), followed by the United States (3,993), Japan (3,296), and South Korea (1,937).

Table 2 The top 10 countries and institutes contributed to publications in hepatocellular carcinoma research.

Rank	Country/Region	Count	Institute	Count
1	China	10,755	Fudan University	1,029
2	United States	3,993	Sun Yat-Sen University	813
3	Japan	3,296	Second Military Medical University	692
4	South Korea	1,937	Shanghai Jiao Tong University	527
5	Taiwan	1,540	Zhejiang University	475
6	Italy	1,335	University of Hong Kong	383
7	Germany	926	Seoul National University	380
8	France	729	Yonsei University	359
9	England	452	Chinese University of Hong Kong	356
10	Spain	433	Sungkyunkwan University	348

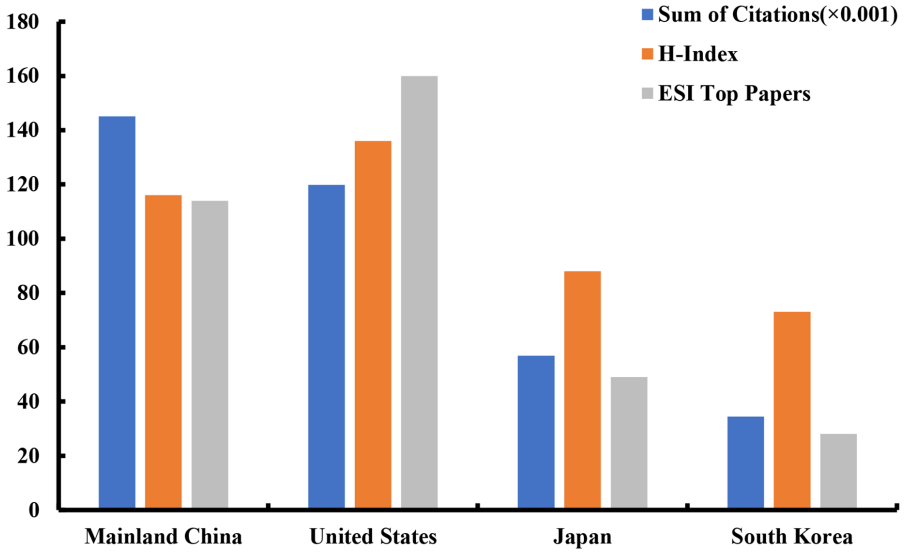

Figure 5 The distribution of ESI top papers, H-index, and citation (×0.001) in the top four countries.
Full-size DOI: 10.7717/peerj.5477/fig-5

Nearly 11,000 institutes (Dataset S3) made contributions to HCC research. The collaborations between institutes were not evident (Fig. 4B), compared to countries. The top 10 institutes (Table 2) contributed more than 20% of total publications. In the list, Fudan University ranked first, followed by Sun Yat-Sen University, Second Military Medical University and Shanghai Jiao Tong University.

Analysis of ESI top papers, H-index, and citations

Among the top four productive countries (Fig. 5), the United States contributed the most number of ESI top papers (160) and achieved the highest H-index value (136). Due to a vast amount of literature, China owned the most citation counts (145,060). The other two countries, Japan and South Korea, did not have advantages in the ranking of the three items mentioned above.

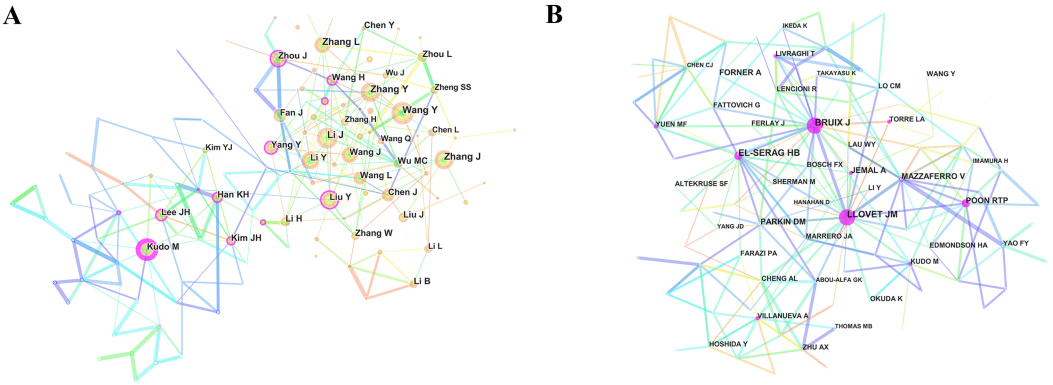

Figure 6 **The distribution of authors.** (A) The network map of active authors contributed to hepatocellular carcinoma research. (B) The network map of co-cited authors contributed to hepatocellular carcinoma research.

Full-size DOI: 10.7717/peerj.5477/fig-6

Table 3 **The top 10 authors, co-cited authors, and co-cited references in hepatocellular carcinoma research.**

Rank	Author	Count	Co-cited Author	Count	Co-cited Reference	Count
1	Wang Y	297	Llovet JM	7,351	Bruix J, 2011, Hepatology, V53, P1020	1,730
2	Li J	291	Bruix J	5,946	Jemal A, 2011, CA-Cancer J Clin, V61, P69	1,578
3	Zhang Y	279	EL-Serag HB	5,038	Llovet JM, 2012, J Hepatol, V56, P908	1,206
4	Zhang J	264	Parkin DM	2,769	Forner A, 2012, Lancet, V379, P1245	1,196
5	Zhang L	254	Jemal A	2,363	Llovet JM, 2008, New Engl J Med, V359, P378	1,193
6	Li Y	240	Poon RTP	2,042	Cheng AL, 2009, Lancet Oncol, V10, P25	855
7	Fan J	237	Forner A	2,010	EL-Serag HB, 2011, New Engl J Med, V365, P1118	825
8	Wang J	235	Mazaferro V	1,950	Torre LA, 2015, CA-Cancer J Clin, V65, P87	721
9	Liu Y	226	Cheng AL	1,614	EL-Serag HB, 2007, Gastroenterology, V132, P2557	674
10	Zhou J	225	Lencioni R	1,559	EL-Serag HB, 2012, Gastroenterology, V142, P1264	521

Distribution of authors

Over 55,900 authors (Dataset S4) contributed to HCC research. Figure 6A showed the collaboration network between authors. Among the top 10 contributive authors (Table 3), Wang Y (297 publications) was ranked first, followed by Li J (291 publications), Zhang Y (279 publications) and Zhang J (264 publications).

CiteSpace analysed the information of author citations and visualized it in a co-citation network (Fig. 6B). Among the top 10 co-cited authors (Table 3, Fig. S2), Llovet JM (7,351 co-citations) was ranked first, followed by Bruix J (5,946 co-citations), EL-Serag HB (5,038 co-citations) and Parkin DM (2,769 co-citations).

Analysis of references

We used CiteSpace IV to construct a network of co-cited references (Fig. 7A) that revealed the relevance between papers. The values of Modularity Q and Mean Silhouette both were more than 0.5 (Fig. S3), indicating that the distributivity and homogeneity of clusters were reasonable and acceptable. All clusters were named after terms extracted from the

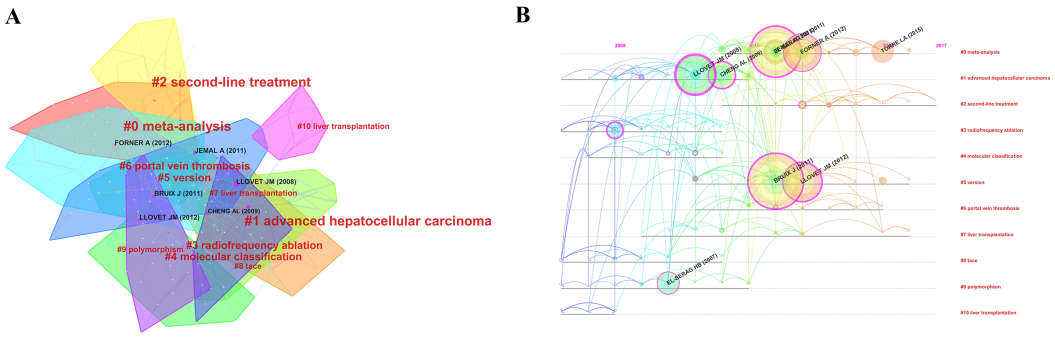

Figure 7 The analysis of references. (A) The co-citation map of references from publications in hepatocellular carcinoma research. (B) The timeline view of co-cited references from publications in hepatocellular carcinoma research.

Full-size DOI: 10.7717/peerj.5477/fig-7

references of publications (Fig. S4). In this network, the first massive cluster was named "#0 meta-analysis", followed by the second, named "#1 advanced hepatocellular carcinoma", and the third, named "#2 second-line treatment." Furthermore, the timeline view of these clusters was shown in Fig. 7B.

Analysis of burst keywords

We identified keywords with strong citation bursts through CiteSpace IV (Fig. 8, Fig. S5). Among them, the keywords that had citation bursts after 2014 were listed as follows: "overexpression" (2014–2015), "delivery" (2014–2015), "cancer stem cell" (2015–2017), "epithelial-mesenchymal transition" (2015–2017), and "transarterial chemoembolization" (2015–2017).

DISCUSSION

General information

At the beginning of the study, we searched for HCC-related papers published from 2000 to 2017 in the Web of Science. The overall trend of publications between 2000 and 2007 was stable, with only slowly increasing (Fig. S6). The total number of publications during this period was relatively small, compared with the later period (2008–2017). For this study, we were committed to identify a trend that has obvious changes in the number of publications. Besides to including a sufficient number of articles, the time span cannot be too long, either, we finally determined to limit the search from 2008 onwards. In relation to the top 15 academic journals, two journals, *Hepatology* (IF 2016 = 13.246) and *Journal of Hepatology* (IF 2016 = 12.486) had an IF higher than 10; two others, *Oncotarget* (IF 2016 = 5.168) and *Cancer Letters* (IF 2016 = 6.375) had an IF between 10 and five; five journals, *World Journal of Gastroenterology* (IF 2016 = 3.365), *Tumor Biology* (IF 2016 = 3.650), *Journal of Gastroenterology and Hepatology* (IF 2016 = 3.452), *Liver International* (IF 2016 = 4.116), and *BMC Cancer* (IF 2016 = 3.288) had an IF between five and three. Furthermore, academic journals with a high IF (higher than three) accounted for 16.86% (N = 4,103) of total publications.

Keywords	Year	Strength	Begin	End	2008 - 2017
adjuvant chemotherapy	2008	3.1865	2008	2009	
interferontherapy	2008	2.5266	2008	2011	
shunt	2008	2.5569	2008	2011	
disease meld score	2008	3.4363	2008	2010	
functional genomics	2008	2.8343	2008	2009	
carcinoma cell	2008	2.6995	2008	2010	
transgenic mice	2008	2.5389	2008	2011	
randomized controlled trial	2008	2.8837	2008	2010	
intrahepatic recurrence	2008	3.7216	2008	2010	
internal radiation therapy	2008	3.0436	2008	2011	
phase ii trial	2008	5.0216	2010	2013	
messenger rna	2008	2.8022	2010	2012	
cirrhotic patient	2008	2.7825	2010	2011	
transplantation	2008	6.713	2010	2012	
marker	2008	3.071	2010	2011	
methylation	2008	6.341	2010	2011	
chronic hepatitis c	2008	2.5696	2012	2013	
polymorphism	2008	3.9715	2012	2014	
chemoprevention	2008	2.5204	2012	2014	
hypoxia	2008	2.5122	2012	2013	
overexpression	2008	2.6983	2014	2015	
delivery	2008	2.6194	2014	2015	
cancer stem cell	2008	3.7038	2015	2017	
epithelial mesenchymal transition	2008	7.1471	2015	2017	
transarterial chemoembolization	2008	6.5943	2015	2017	

Figure 8 **The keywords with the strong citation bursts in articles related to hepatocellular carcinoma research published from 2008 to 2017.**

Full-size DOI: 10.7717/peerj.5477/fig-8

Among the top 10 contributive countries/regions in HCC research, China was the only one from the developing world, showing its vast progress in life science over the past decade. China had an absolute advantage in the number of papers published, which also received a large number of citations. However, the United States occupied the first positions in both ESI top papers and H-index. In terms of research quality, the United States was the dominant country in HCC research. The most active collaborations were observed between Saudi Arabia and Egypt, Australia and Scotland and England and Brazil. Moreover, the collaborations among European countries were much stronger than those among Asian countries.

The top 10 institutes contributed to 5,362 papers, which accounted for 22.03% of total publications. In this list, the top five institutes were all from China. Additionally, there were 3,994 Chinese institutes involved in HCC research (Dataset S3), accounting for 36.34% of the total number of research institutes worldwide. According to recent reports, China accounted for more than half of world's HCC patients, including over 466,000 new cases in 2015 (*Zhu et al., 2016*). The estimated incidence rate of HCC was 30.62 per 100,000 standard population, resulting it as the second common malignancy in China (*Tanaka et al., 2011*). Except for that, there are limited treatment options for unresectable HCC patients and the overall prognosis of HCC is very poor (*Xie et al., 2017*), making it a serious health issue in current China. That is the reason why a considerable number of Chinese institutes engaged in HCC research and China leads in the number of papers published.

Citation information

Among the top 10 active authors, each person has published at least 225 papers; they were regarded as prolific authors. Despite that, none of them are included as top co-cited authors, suggesting that prolific authors should focus not only on number of publications but also quality of research. Regarding co-cited authors, those with more than 5,000 co-citations, including Llovet JM, who discovered the critical role of mTOR signaling in HCC pathogenesis (*Villanueva et al., 2008*), Bruix J, who provided guidelines for HCC management (*Bruix & Sherman, 2011*) and EL-Serag HB, who elaborated the epidemiology of HCC and viral hepatitis (*El-Serag, 2012*), have made significant contributions in this field.

The co-citation clusters in the timeline view demonstrated that top co-cited references were mainly gathered between 2008 and 2012. Meanwhile, among the top 100 co-cited references identified by CiteSpace IV, there were 72 items existed in the period from 2008 to 2012 (Fig. S4). Given this result, the period (2008–2012) could be considered as a "golden phase" of HCC research within the past decade. Table 3 presented the top 10 co-cited references in HCC research. Bruix J (2011), who published a paper in *Hepatology*, had the highest co-citations (1730), followed by Jemal A (2011, 1,578 co-citations), Llovet JM (2012, 1,206 co-citations) and Forner A (2012, 1,196 co-citations), who published papers in *CA: A Cancer Journal for Clinicians*, *Journal of Hepatology* and *The Lancet* respectively. Additionally, other journals with highest impact factor have also contributed some papers on HCC research during the past decade (Dataset S1), such as *New England Journal of Medicine* (5 papers), *The Lancet* (12 papers), *Nature* (10 papers), and *Cell* (nine papers). They were the fundamentals of this field.

Research frontiers

We used CiteSpace IV to capture the burst keywords, which could be considered a prediction of research frontiers. As shown in Fig. 8, the blue line represented the time intervals and the red line represented the period of citation bursts. Here, we listed three frontiers of HCC research as follows:

i. Transarterial chemoembolization: Transarterial chemoembolization (TACE) is considered as an effective treatment for intermediate or advanced HCC patients (*Han & Kim, 2015*). In the United States, TACE is not only the most common therapy for HCC patients but also the most common bridging therapy for patients waitlisted for liver transplantation (*Shah et al., 2011*; *Thuluvath et al., 2010*). According to a retrospective study of the SEER database, TACE utilization significantly improved survival for HCC patients, especially those at an intermediate stage (*Gray et al., 2017*). Additionally, a recent study has proved that TACE can be a useful treatment option for HCC patients with segmental portal vein tumour thrombus (*Choi et al., 2017*).

ii. Epithelial-mesenchymal transition: Epithelial-mesenchymal transition (EMT) is a biological process in which epithelial cells gradually change into a mesenchymal-like type (*Van Zijl et al., 2009*). This process has proved to be involved in various pathological conditions, including inflammation, fibrosis and cancer (*Barriere et al., 2015*; *Skrypek et al., 2017*). Increasing evidence demonstrated that EMT plays a vital role in transferring malignant hepatocytes during the progression of HCC (*Giannelli et al., 2016*; *Huaman et al., 2018*; *Nitta et al., 2008*). The association between EMT and HCC raises a demand to exploit novel diagnostic and therapeutic strategies against HCC progression.

iii. Cancer stem cell: Solid tumours contain a small fraction of tumorigenic cells, known as cancer stem cells (CSCs) (*Valent et al., 2012*). CSCs play a crucial role in tumour metastasis/recurrence and have been identified in many malignant tumours, including HCC (*Valent et al., 2012*). Accumulating studies have illustrated that HCC CSCs could be enriched by several different markers, including CD133, CD90, CD24, CD13 and EpCAM (*Feng et al., 2014*; *Kim & Park, 2014*; *Sainz Jr & Heeschen, 0000*). HCC CSCs could partially explain the heterogeneity of HCC, metastasis after hepatic tumour resection and chemotherapeutic resistance in advanced HCC cells (*Ji & Wang, 2012*; *Zheng et al., 2018*), which provide the potential to develop novel therapeutic strategies based on stem cell biology.

Strengths and limitations

To the best of our understanding, this paper is the first bibliometric analysis on HCC research trend over the past decade. The data analysis process was relatively objective. However, most publications retrieved from the database were written in English, causing incomplete analysis to some extent. Furthermore, this study consisted exclusively of original and review articles published between 2008 and 2017 and indexed by the Web of Science. It may not be enough to represent all HCC literature, such as other document types published in journals, books, and conferences were not included. The analysis in this study was based on articles recorded in the Science Citation Index-Expanded (SCI-E) of the Web

of Science Core Collection (WoSCC). Each journal to which the SCI-E articles belong had its corresponding citation report provided by the Web of Science. Although other databases such as PubMed, Scopus, and Embase could provide a broader range of coverage, much of the "extra coverage" could be attributed to journals with potentially limited readers. Given that our objective was to conduct a high-quality bibliometric analysis to identify research trends in the core of HCC field, the SCI-E articles from WoSCC may be the only appropriate choice. Therefore, the results from other databases were not included. As for China ranked first in publications, except for the active participation of Chinese institutes, the strong support of science funding in China could be another important reason. A recent study has shown that the proportion of funded papers in China is the highest, compared to other countries. Nearly 80% of SCI-E papers are supported by science funding (*Sun et al., 2013*). Therefore, the advantage of the number of publications from China is particularly prominent, which may create an illusion that the gap between western countries and China is widening. Finally, although the Web of Science database is still updating, this study covers the vast majority of papers in HCC research since 2008; new data may not influence the final results.

CONCLUSIONS

The number of publications in HCC research has been increasing over the past decade. The United States, Japan, and China were the top three countries contributing to HCC studies. There were active collaborations between developed countries. Although many Chinese institutes were engaged in HCC research, the United States was still the dominant country. Llovet JM, Bruix J and EL-Serag HB may be ideal candidates for academic cooperation. Transarterial chemoembolization, epithelial-mesenchymal transition and cancer stem cell may be frontiers in this field, and researchers should pay close attention to relevant studies in the coming years.

ACKNOWLEDGEMENTS

The authors would like to thank the editor and anonymous reviewers for their contributions to improving the quality of this paper. We would also like to thank PaperTrue for editing and proofreading this manuscript.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

This work was supported by the National Natural Science Foundation of China (No. 81573191). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Yan Miao conceived and designed the experiments, performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Ying Zhang performed the experiments, analyzed the data, contributed reagents/materials/analysis tools, approved the final draft.
- Lihong Yin conceived and designed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.

Data Availability

The following information was supplied regarding data availability:

Figshare: http://figshare.com/articles/Raw_data_for_Trends_in_hepatocellular_carcinoma_from_2008_to_2017_A_bibliometric_analysis_/6885119.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.5477#supplemental-information.

REFERENCES

Aggarwal A, Lewison G, Idir S, Peters M, Aldige C, Boerckel W, Boyle P, Trimble EL, Roe P, Sethi T, Fox J, Sullivan R. 2016. The state of lung cancer research: a global analysis. *Journal of Thoracic Oncology* **11**:1040–1050 DOI 10.1016/j.jtho.2016.03.010.

Almeida-Guerrero A, Olaya-Gomez JC, Sanchez-Ramirez N, Murillo-Garcia DR, Cardona-Ospina JA, Lagos-Grisales GJ, Rodriguez-Morales AJ. 2018. Mitigation of the global impact of Lassa fever: have we investigated enough about this Arenavirus?—a bibliometric analysis of Lassa Fever research. *Travel Medicine and Infectious Disease* DOI 10.1016/j.tmaid.2018.06.012.

Azer SA. 2015. The top-cited articles in medical education: a bibliometric analysis. *Academic Medicine* **90**:1147–1161 DOI 10.1097/acm.0000000000000780.

Baek S, Yoon DY, Lim KJ, Cho YK, Seo YL, Yun EJ. 2018. The most downloaded and most cited articles in radiology journals: a comparative bibliometric analysis. *European Radiology* **28**:1–7 DOI 10.1007/s00330-018-5423-1.

Balogh J, Victor D, Asham EH, Burroughs SG, Boktour M, Saharia A, Li X, Ghobrial RM, Monsour HP. 2016. Hepatocellular carcinoma: a review. *Journal of Hepatocellular Carcinoma* **3**:41–53 DOI 10.2147/JHC.S61146.

Barriere G, Fici P, Gallerani G, Fabbri F, Rigaud M. 2015. Epithelial mesenchymal transition: a double-edged sword. *Clinical and Translational Medicine* **4**:Article 14 DOI 10.1186/s40169-015-0055-4.

Bruggmann D, Pulch K, Klingelhofer D, Pearce CL, Groneberg DA. 2017. Ovarian cancer: density equalizing mapping of the global research architecture. *International Journal of Health Geographics* **16**:Article 3 DOI 10.1186/s12942-016-0076-2.

Bruix J, Sherman M. 2011. Management of hepatocellular carcinoma: an update. *Hepatology* **53**:1020–1022 DOI 10.1002/hep.24199.

Chen C. 2004. Searching for intellectual turning points: progressive knowledge domain visualization. *Proceedings of the National Academy of Sciences of the United States of America* **101(Suppl 1)**:5303–5310 DOI 10.1073/pnas.0307513100.

Choi JW, Kim HC, Lee JH, Yu SJ, Kim YJ, Yoon JH, Jae HJ, Hur S, Lee M, Chung JW. 2017. Transarterial chemoembolization of hepatocellular carcinoma with segmental portal vein tumour thrombus. *European Radiology* **27**:1448–1458 DOI 10.1007/s00330-016-4511-3.

Costas R, Bordons M. 2007. The h-index: advantages, limitations and its relation with other bibliometric indicators at the micro level. *Journal of Informetrics* **1**:193–203 DOI 10.1016/j.joi.2007.02.001.

Dalpé R. 2002. Bibliometric analysis of biotechnology. *Scientometrics* **55**:189–213 DOI 10.1023/A:1019663607103.

El-Serag HB. 2012. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* **142**:1264–1273. DOI 10.1053/j.gastro.2011.12.061.

El-Serag HB, Kanwal F. 2014. Epidemiology of hepatocellular carcinoma in the United States: where are we? where do we go? *Hepatology* **60**:1767–1775 DOI 10.1002/hep.27222.

Ellegaard O, Wallin JA. 2015. The bibliometric analysis of scholarly production: how great is the impact? *Scientometrics* **105**:1809–1831 DOI 10.1007/s11192-015-1645-z.

Feng D, Wang N, Hu J, Li W. 2014. Surface markers of hepatocellular cancer stem cells and their clinical potential. *Neoplasma* **61**:505–513 DOI 10.4149/neo_2014_061.

Garfield E. 2006. The history and meaning of the journal impact factor. *Journal of the American Medical Association* **295**:90–93 DOI 10.1001/jama.295.1.90.

Ghouri YA, Mian I, Rowe JH. 2017. Review of hepatocellular carcinoma: epidemiology, etiology, and carcinogenesis. *Journal of Carcinogenesis* **16**:Article 1 DOI 10.4103/jcar.JCar_9_16.

Giannelli G, Koudelkova P, Dituri F, Mikulits W. 2016. Role of epithelial to mesenchymal transition in hepatocellular carcinoma. *Journal of Hepatology* **65**:798–808 DOI 10.1016/j.jhep.2016.05.007.

Gray SH, White JA, Li P, Kilgore ML, Redden DT, Abdel Aal AK, Simpson HN, McGuire B, Eckhoff DE, Dubay DA. 2017. A SEER database analysis of the survival advantage of transarterial chemoembolization for hepatocellular carcinoma: an underutilized therapy. *Journal of Vascular and Interventional Radiology* **28**:231–237 e232 DOI 10.1016/j.jvir.2016.09.022.

Han K, Kim JH. 2015. Transarterial chemoembolization in hepatocellular carcinoma treatment: barcelona clinic liver cancer staging system. *World Journal of Gastroenterology* **21**:10327–10335 DOI 10.3748/wjg.v21.i36.10327.

Hefaiedh R, Ennaifer R, Romdhane H, Ben Nejma H, Arfa N, Belhadj N, Gharbi L, Khalfallah T. 2013. Gender difference in patients with hepatocellular carcinoma. *Tunisie Medicale* **91**:505–508.

Huaman J, Bach C, Ilboudo A, Ogunwobi OO. 2018. Epithelial-to-mesenchymal transition in hepatocellular carcinoma. In: Liu C, ed. *Precision molecular pathology of liver cancer*. Cham: Springer International Publishing, 131–152.

Ji J, Wang XW. 2012. Clinical implications of cancer stem cell biology in hepatocellular carcinoma. *Seminars in Oncology* **39**:461–472 DOI 10.1053/j.seminoncol.2012.05.011.

Khan NR, Saad H, Oravec CS, Norrdahl SP, Fraser B, Wallace D, Lillard JC, Motiwala M, Nguyen VN, Lee SL, Jones AV, Ajmera S, Kalakoti P, Dave P, Moore KA, Akinduro O, Nyenwe E, Vaughn B, Michael LM, Klimo Jr P. 2018. An analysis of publication productivity during residency for 1506 neurosurgical residents and 117 residency departments in North America. *Neurosurgery* **83**:217–227 DOI 10.1093/neuros/nyy217.

Kim H, Park YN. 2014. Hepatocellular carcinomas expressing 'stemness'-related markers: clinicopathological characteristics. *Digestive Diseases* **32**:778–785 DOI 10.1159/000368021.

Massarweh NN, El-Serag HB. 2017. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Cancer Control* **24**: 1073274817729245 DOI 10.1177/1073274817729245.

Mittal S, El-Serag HB. 2013. Epidemiology of HCC: consider the population. *Journal of Clinical Gastroenterology* **47**:S2–S6 DOI 10.1097/MCG.0b013e3182872f29.

Nitta T, Kim JS, Mohuczy D, Behrns KE. 2008. Murine cirrhosis induces hepatocyte epithelial mesenchymal transition and alterations in survival signaling pathways. *Hepatology* **48**:909–919 DOI 10.1002/hep.22397.

Pritchard A. 1969. Statistical bibliography or bibliometrics. *Journal of Documentation* **25**:348–349.

Ramos J. 2003. Using tf-idf to determine word relevance in document queries. In: *Proceedings of the first instructional conference on machine learning. Available at http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.121.1424&rep=rep1&type=pdf* .

Sainz Jr B, Heeschen C. Standing out from the crowd: cancer stem cells in hepatocellular carcinoma. *Cancer Cell* **23**:431–433 DOI 10.1016/j.ccr.2013.03.023.

Shah SA, Smith JK, Li Y, Ng SC, Carroll JE, Tseng JF. 2011. Underutilization of therapy for hepatocellular carcinoma in the medicare population. *Cancer* **117**:1019–1026 DOI 10.1002/cncr.25683.

Skrypek N, Goossens S, De Smedt E, Vandamme N, Berx G. 2017. Epithelial-to-Mesenchymal transition: epigenetic reprogramming driving cellular plasticity. *Trends in Genetics* **33**:943–959 DOI 10.1016/j.tig.2017.08.004.

Sun JW, Liu D, Wang XW, Hou HY. 2013. Science funding and SCI papers output: a comparative analysis on 10 countries. *Studies in Science of Science* **31**:36–42.

Tanaka M, Katayama F, Kato H, Tanaka H, Wang J, Qiao YL, Inoue M. 2011. Hepatitis B and C virus infection and hepatocellular carcinoma in China: a review of epidemiology and control measures. *Journal of Epidemiology* **21**:401–416 DOI 10.2188/jea.JE20100190.

Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. 2010. Liver transplantation in the United States, 1999–2008. *American Journal of Transplantation* **10**:1003–1019 DOI 10.1111/j.1600-6143.2010.03037.x.

Valent P, Bonnet D, De Maria R, Lapidot T, Copland M, Melo JV, Chomienne C, Ishikawa F, Schuringa JJ, Stassi G, Huntly B, Herrmann H, Soulier J, Roesch

A, Schuurhuis GJ, Wohrer S, Arock M, Zuber J, Cerny-Reiterer S, Johnsen HE, Andreeff M, Eaves C. 2012. Cancer stem cell definitions and terminology: the devil is in the details. *Nature Reviews Cancer* **12**:767–775 DOI 10.1038/nrc3368.

Van Zijl F, Zulehner G, Petz M, Schneller D, Kornauth C, Hau M, Machat G, Grubinger M, Huber H, Mikulits W. 2009. Epithelial-mesenchymal transition in hepatocellular carcinoma. *Future Oncol* **5**:1169–1179 DOI 10.2217/fon.09.91.

Villanueva A, Chiang DY, Newell P, Peix J, Thung S, Alsinet C, Tovar V, Roayaie S, Minguez B, Sole M, Battiston C, Van Laarhoven S, Fiel MI, Di Feo A, Hoshida Y, Yea S, Toffanin S, Ramos A, Martignetti JA, Mazzaferro V, Bruix J, Waxman S, Schwartz M, Meyerson M, Friedman SL, Llovet JM. 2008. Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology* **135(1983)**:1972–1983. e1971-1911 DOI 10.1053/j.gastro.2008.08.008.

Wakeling S, Willett P, Creaser C, Fry J, Pinfield S, Spezi V. 2017. Transitioning from a conventional to a 'mega'journal: a bibliometric case study of the journal medicine. *Publications* **5**:Article 7 DOI 10.3390/publications5020007.

White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. 2017. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology* **152**:812–820 DOI 10.1053/j.gastro.2016.11.020.

Xie D-Y, Ren Z-G, Zhou J, Fan J, Gao Q. 2017. Critical appraisal of Chinese 2017 guideline on the management of hepatocellular carcinoma. *Hepatobiliary Surgery and Nutrition* **6**:387–396 DOI 10.21037/hbsn.2017.11.01.

Zheng H, Pomyen Y, Hernandez MO, Li C, Livak F, Tang W, Dang H, Greten TF, Davis JL, Zhao Y, Mehta M, Levin Y, Shetty J, Tran B, Budhu A, Wang XW. 2018. Single cell analysis reveals cancer stem cell heterogeneity in hepatocellular carcinoma. *Hepatology* **68**:127–140 DOI 10.1002/hep.29778.

Zhu RX, Seto W-K, Lai C-L, Yuen M-F. 2016. Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region. *Gut and Liver* **10**:332–339 DOI 10.5009/gnl15257.