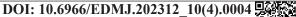
Original Article





Trends of Treatments of Hepatocellular Carcinoma in Recent 3-Decade Based on the Top-100 Influential Articles from Taiwan

Chen-Guo Ker^{1,2,*}, Jen-Lung Chen^{1,*}, Yaw-Sen Chen¹

Objective: The prevalence of liver cancer is still high in Taiwan and remained flat epidemiological curve in recent decades despite improvements in hepatitis and cancer surveillance programs. Therefore, we designed this study using bibliometric citation analysis to outline the trends of treatments of hepatocellular carcinoma (HCC) patients in Taiwan.

Methods: The Web of Science Core Collection Database searched interrelated articles published from 1992 to 2021, and divided into 1st, 2nd, and 3rd decades. Taiwan Top-100 articles were selected based on the yearly highest-ranking cited times and limited in the studies of treatment.

Results: Total of 38,838 articles on clinical studies of liver cancer were observed in our search. The top numbers of articles from the Top-10 countries were analyzed in which China ranked the first, followed by the United States of America, and Japan among 144 countries. Moreover, 1,833 (4.72%) articles published from Taiwan ranking as the 9th in the world. The contributions of these 1,833 articles were reported by 202 institutions of Taiwan. The numbers of articles were published 127 (6.9%), 461 (25.2%) and 1,245 (67.9%) in the 1st, 2nd and 3rd decades respectively. Taiwan Top-100 articles were averagely selected and limited in treating patients with hepatocellular carcinoma. The treatment methods were found 66.7% with hepatic resection and 33.3% with transhepatic artery chemo-embolization in 1992 – 2001. After 2002, multiple treatment methods could be applied, including target therapy and immune cell therapy. Publications concerning hepatectomy decreased in publications from 66.7%, 25.7% to 13.5% in the periods of 1992 – 2001, 2002 – 2011, and 2012 – 2021 respectively. In contrary, target and immunotherapy were markedly increased with 29.7% and 18.9% among all treatment methods in 2012 – 2021.

Conclusions: Clinical studies were actively conducted in Taiwan because of the burden of liver diseases. Surgical resection and regional ablation were the main in the 1st and 2nd decades and decreased in publications gradually. Molecular targeted agent therapy and immunotherapy were sprung into a half territory of publications concerning the clinical treatment of HCC after 2012 in Taiwan.

Key words: hepatocellular carcinoma, treatment, surgery, Taiwan

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Introduction

The Taiwan Cancer Registration System documented that the crude incidence rate of liver cancer had remained high and resulted in 61.92, 66.62, 67.32, and 66.27 per 10⁵ persons for 2005, 2010, 2015, and 2019 respectively in male.1 The crude mortality rate was 45.82 for male and 21.16 for female per 10⁵ persons per year recorded in 2019. The leading cause of death was the 2^{nd} in male and 4^{th} in female among all cancer deaths in recent years in Taiwan.1 Therefore, liver cancer still remains a poor prognosis with a critical public health issue despite improvements in hepatitis control and care program through anti-viral therapy and successful vaccination project in Taiwan. The age-adjusted incidence rates (> 20 per 10^5 persons) were high in East Asia (China, Korea, and Vietnam) and Sub-Saharan Africa.² About three quarters of liver cancer patients occur in Asia, especially in China, accounting for more than half of the world's burden.³ Actually, liver cancer is still a world health issue and a total of 841,000 (4.7%) new hepatocellular carcinoma (HCC) patients are estimated, and another 782,000 (8.2%) HCC-related deaths were reported globally in 2018.⁴ Hence, we have to care about the high mortality of liver cancer, the fourth leading cause of cancer death globally.

HCC accounts for 75% – 85% of liver cancers worldwide and the main risk factors for HCC are chronic hepatitis B/C virus (HBV or HCV) infection, aflatoxin-contamination, alcohol intake, and others.⁵ The treatments were based on the guidelines, which were adapted and modified in each country and try to assist surgeons and physicians in managing HCC patients.^{2,6-9} Clinical selection of treatment strategy was limited early in 1992 to 2001 (1st decade) in Taiwan or even in the world. The devolution of HCC treatment over the past 30 years is difficult to chronicle the evaluation of each treatment method for HCC in Taiwan. Liver resection and transhepatic artery chemoembolization (TACE) were commonly used for treatments for liver cancer before 1990. Then, regional local ablation with percutaneous pure alcohol injection, micro-wave thermo-ablation, or radio-frequency ablation (RFA) were applied in the treatment.¹⁰ Multiple choice treatments including surgical or non-surgical management have been available depending on the patient's condition around the year of 2000 in Taiwan.

With the aid of bibliometric citation analysis, a broadly used method was mapped to provide an information on the trends in HCC treatments. The citation numbers of an article indicate the importance of their study and directly influence the trends and understanding of the treatments for HCC patients comprehensively.^{11,12} Newly reported technologies in the articles were popular for a short period but sometimes disappeared from practice shortly. However, in the recent decade, some new and effective tools have been explored such as target or immune therapy. Some traditional or modernized clinical practices still had been recognized as methods for leading to long-standing improvement in the patient care program.¹³⁻¹⁵

In this study, published articles about liver cancer were analyzed and the number of articles was ranked by countries or regions in the world. Moreover, the trends of treatment for HCC patients were evaluated and illustrated through the selected most cited Top-100 articles over the past three decades in Taiwan. Therefore, we established this study by using bibliometric citation analysis to outline the devolution of treatments for HCC patients in Taiwan.

Materials and Methods

Literature search and screening

A systemic literature from Clarivate Analytics Web of Science Core Collection Database was searched for articles published in the recent three decades from January 1992 to December 2021. We used the following keyword subgroup #1 included hepatocellular carcinoma, liver cancer, hepatic cancer, hepatic cell carcinoma, HCC, hepatoma, or hepatic malignancy. Subgroup #2 included hepatectomy, hepatectic resection, liver resection, liver surgery, liver transplantation, trans-catheter arterial chemo-embolization, trans-arterial embolization (TAE), hepatic artery continuous infusion (HAI), hepatic artery infusion chemotherapy, radiofrequency ablation, microwave ablation, RFA, chemotherapy, targeted therapy. radiotherapy, external radiotherapy, internal radiotherapy, stereotactic body radiation therapy (SBRT), selective internal radiation therapy, SBRT, selective internal radiotherapy (SIRT), trans-arterial radio-chemoembolization, Yitrium 90, Y-90, CAR-T, immunotherapy, or immune-cell therapy. The last, subgroup #3 included survival rate, or disease free survival rate, prognosis, outcome, morbidity, mortality, or complication. Finally, these three subgroups of keywords were used for searching the list of articles published and assessed on the day April 14, 2022. We focused on clinical studies of liver cancer in adult patients, which were written in the English language. We excluded conference proceeding paper and systemic review, meeting abstract and editorial letters. Then, the articles were divided by the study sites: worldwide vs. Taiwan. Among the original articles on the clinical treatment of HCC in adult patients, Top-100 articles from Taiwan were identified and exclusion criteria were previous double publications with the same treatment method, case report, systemic review or guideline, animal model, and cell line study. Taiwan Top-100 articles were identified based on the citation times and average distribution of papers published each year from 1992 to 2021 and divided into three periods; the 1st decade (1992 – 2001), 2nd decade (2002 – 2011) and 3rd decade (2012 – 2021) (Table 1). The selected Taiwan Top-100 articles showed the ranking of times cited articles published in each represented year from Taiwan (eTable 1 in the <u>Supplement</u>).

Data collection and analyses

We downloaded the Taiwan Top-100 articles based on the higher times cited articles published from Taiwan, including all available information from the Web of Science Core Collection Database (WOS) and PubMed data bank for abstract and full-text. The title, authors, institutions, journal, number of times cited (TC), and year of publication were extracted and analyzed from the bibliometric analysis of WOS. The main topic concerning the treatment methods and article types were determined by reading the title, abstract, or full text if necessary. All of the clinical studies must include the methods of treatment, survival rate or treatment responsive rate. Basic profiles

Period of year	*No. of articles total	No. of articles selected per year	Times cited (Mean, range)	Selection rate being Top-100
1992 - 2001	127	$10 (1 \times 10 \text{ y} = 10)$	87 (29 – 211)	1^{st} decade: $10/127 = 7.9\%$
2002 - 2007	211	$13 (2 \times 6 y + 1 = 13)$	107.9 (26 - 480)	2^{nd} decade: 27/444 = 6.1%
2008 - 2011	233	$14 (3 \times 4 y + 2 = 14)$	361.9 (20 - 3,945)	
2012 - 2014	284	$16 (5 \times 3 y + 1 = 16)$	191.6 (12 - 633)	$3^{\rm rd}$ decade: 63/1,262 = 5.0%
2015 - 2018	447	$24 (6 \times 4 y = 24)$	171.2 (5 – 1,967)	
2019 - 2020	317	$14 (7 \times 2 y = 14)$	113.4 (29 – 683)	
2021	214	9	10.4 (4 - 28)	
Total	1,833	100	162 (4 - 3,945)	100/1,833 = 5.5%

Table 1. Taiwan Top-100 influential articles concerning the treatment of HCC based on the ranking of times cited from Web of Science reported from Taiwan (1992 – 2021).

Data from Web of Science accessed date of April 2022.

of publications of HCC in adult patients were analyzed using a spreadsheet.

Results

Top-10 countries publication concerning liver cancer in the world

A total of 38,838 articles was observed by searching with the keywords published from the world. The number of article of the Top-10 countries were recorded and ranked based on their numbers of articles from reported country. The top one was China (12,174; 31.3%), followed by USA (10,129; 26.1%), and Japan (6,479; 16.9%) among 144 countries in the world as shown in the Figure 1. There were 1,833 (4.72%) articles published from Taiwan with the 9th rank in the world.

Contributions of institutions and published journals of articles from Taiwan Top-100 in recent 3 decades

The contributions of 1,833 articles were

reported from 202 institutions in Taiwan. Among them, 127 (6.9%), 444 (24.2%) and 1,262 (68.9%) articles were published in the 1st, 2nd and 3rd decades respectively. The distributions and numbers of articles in 3-decade period were demonstrated in Table 1. Taiwan Top-100 articles were observed in 7.9% (10/127), 6.1% (27/444), and 5.0% (63/1,262) for the 1st, 2nd and 3rd decades based on both the number of articles and the ranking of TC in each year. Moreover, Taiwan Top-100 articles were averagely selected and focusing on the clinical field of intervention methods for HCC patients in order to outline the trends of the treatment methods in recent 3 decades in Taiwan.

Top-30 institutions among 202 institutions totally in Taiwan and the numbers of their published articles were illustrated in Table 2. Among them, the first was Chang Gung Memorial Hospital and University (632 and 516 articles) and others were listed in Table 2. Top-30 journals out of 187 journals published

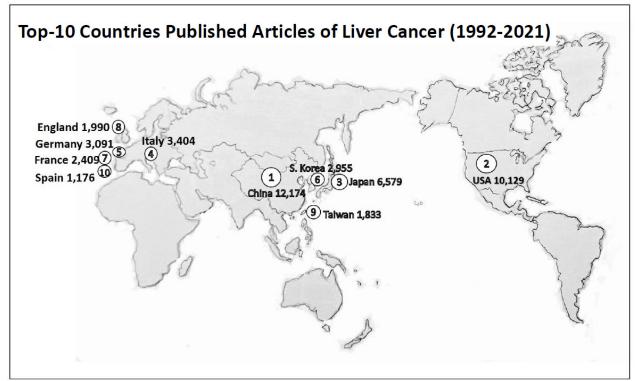


Fig. 1 Geographic distribution of articles of liver cancer published from the Top-10 countries and demonstrated the numbers of published articles and ranking in the world in recent three decades.

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Ranking	Institution [*]	Number of articles	
1 & 3	Chang Gung Memorial Hospital + University	632 + 516	
2	National Yang Ming Chiao Tung University [†]	534	
4 & 5	National Taiwan University + Hospital	487 + 392	
6	Taipei Veterans General Hospital	328	
7 & 10	China Medical University + Hospital Taiwan	261 + 163	
8 & 13	Kaohsiung Medical University + Hospital	211 + 136	
9 & 29	Taipei Medical University + Hospital	188 + 58	
11 & 17	National Cheng Kung University + Hospital	150 + 103	
12 & 28	Chung Shan Medical University + Hospital	138 + 58	
14	National Health Research Institutes Taiwan	134	
15	Taichung Veterans General Hospital	124	
16 & 18	National Defense Medical Center + Tri SG Hospital	120 + 99	
19	Academia Sinica Taiwan	96	
20	Chi Mei Hospital	78	
21	Buddhist Tzu Chi General Hospital	74	
22	Asia University Taiwan	72	
23	Changhua Christian Hospital	71	
24	Fu Jen Catholic University	71	
25	Mackay Memorial Hospital	67	
26 & 27	I-Shou University + Hospital	66 + 64	
30	Kaohsiung Veterans General Hospital	57	

Table 2. Top-30 institutions among 202 institutions which contributed 1,833 articles totally reported from Taiwan recorded from Web of Science Collection Database.

^{*} More than two institutions of an author's institution in each article.

[†] Authors of these articles were collaborative with the Veteran General Hospital.

for all articles were listed in Table 3, in which three journal's editorial offices located in Taiwan.

Taiwan Top-100 articles

Total of 1,833 articles were published and identified from the Web of Science Core Collection Database. The Taiwan Top-100 most influential articles on the clinical treatment of adult HCC patients were screened according to the article's cited number in each year (Table 1 and eTable 1 in the <u>Supplement</u>). The average times cited number were 162 and ranged from 4 to 3,945 cited scores. Institution of the first author of each article was demonstrated in the Figure 2. Other thirty-six articles (36%) were resulted from co-operative studies with foreign institutions including USA (15 studies), Korea (6), China (3), Japan (3), Spain (3), Singapore (2), UK (2), Germany (1), Italy (1), and Romania (1 study). Types of clinical trials were 3 (8.8%), 12 (35.3%), 15 (44.1%), and 4 (11.8%) for phase I, II, III, and I + II respectively.

Trends of treatment according to the Taiwan Top-100 articles within three decades

The treatment methods included hepatic resection (66.7%) and TACE (33.3%) in the 1st decade (Table 4). After 2002, multiple treatment methods were adopted including target therapy and immune cell therapy (Fig. 3). Articles concerning hepatic resection was decreased from 66.7%, 26.5% to 13.5% in the 1st, 2^{nd} and 3^{rd} decade. On the contrary, target and immunotherapy were beginning and increased by 8.8% to 29.7%, and 2.9% to 18.9% respectively among all treatment methods in the 2^{nd} and 3^{rd} decades (Table 4 & Fig. 3).

Ranking	Name of journal	Number of articles	Impact factor (2020)
1	PLOS ONE	55	3.240
2	J of Formosa Medical Association [*]	54	3.282
3	J of Gastroenterology & Hepatology	54	4.029
4	Hepato-Gastroenterology	53	$0.2~(2022)^{\#}$
5	World J of Gastroenterology	52	5.742
6	Medicine	48	1.889
7	Scientific Reports	44	4.380
8	World J of Surgery	40	3.352
9	Annals of Surgical Oncology	37	5.344
10	Oncotarget	37	5.168 (2016)
11	Cancers	36	6.639
12	Hepatology	30	17.425
13	BMC Cancer	28	4.430
14	J of Hepatology	28	25.083
15	J of Surgical Oncology	27	3.454
16	J of the Chinese Medical Association*	27	2.743
17	Liver International	27	5.828
18	World J of Surgical oncology	26	2.754
19	Transplantation Proceedings	25	1.066
20	Liver Cancer	23	11.740
21	Hepatology International	21	6.047
22	Anticancer Research	18	2.480
23	Cancer	18	6.860
24	Kaohsiung J of Medical Sciences*	18	2.744
25	International J of Radiation Oncology Biology Physics	17	7.038
26	International J of Cancer	16	7.396
27	BMC Gastroenterology	15	3.067
28	Clinical Cancer Research	15	12.531
29	International J of Molecular Sciences	15	5.924
30	J of Gastrointestinal Surgery	15	3.452

Table 3. The Top-30 journals among 187 journals published articles from Taiwan.

* These three journal's editor office were located in Taiwan.

[#] This journal had stopped and renamed Surg, Gastroenterol, Oncol with Site Score 0.2 in 2022.

Discussion

Liver cancer was the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide with approximately 906,000 new cases and high mortality by 830,000 deaths in 2020.⁵ In Taiwan, majority of liver cancers were HCC in pathological diagnosis which accounted for 92.19%, 90.4%, 91.87% and 88.32% in 2005, 2010, 2015 and 2019 respectively. It is still one of the most significant burden nowadays.¹ Moreover, liver cancer studies were extensive worldwide particularly in the high-burden countries, including Eastern Asia. Therefore, China, Japan, Korea, and Taiwan were ranked at the Top-10 of the world for these studies. Among the World Top-100 most influential articles concerned with the management of HCC, the top one in the world was the USA (n = 33 articles), and Taiwan (n = 12 articles) ranked the 8th in a systemic search from 1980 to 2020.¹⁶ In World Top-100 articles were identified with an average of 738 citations (range; 349 – 6,799). However, average cited number was 162 (range; 4 to 3,945) in Taiwan Top-100 from our study.

The most influential 100 articles about the treatment of HCC were selected as Taiwan

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Fig. 2 Hospitals locations and the numbers before the name of each hospital represent the frequency of Taiwan Top-100 publications. Other 36 articles were collaborative with international studies.

Period of articles	1^{st} decade (1992 – 2001)	2^{nd} decade (2002 – 2011)	3^{rd} decade (2012 – 2021)	Total (1992 – 2121)
Method	n (%)	n (%)	n (%)	total (%)
1. Hepatic resection	8 (66.7%)	9 (26.5%)	10 (13.5%)	27 (22.5%)
a. Open	8	8	9	25
b. Laparoscopic		1	1	2
2. RLA		10 (29.5%)	7 (9.5%)	17 (14.2%)
a. RFA		7	6	13
b. PEI		3	1	4
3. TAC	4 (33.3%)	2 (5.9%)	7 (9.5%)	13 (10.8%)
a. TACE	4	2	6	12
b. HAI			1	1
4. Liver transplantation		1 (2.9%)	4 (5.4%)	5 (4.2%)
5. Radio-therapy		3 (8.8%)	9 (12.1%)	12(10.0)
a. EBRT		3	4	7
b. Y-90			4	4
c. Proton bean			1	1
6. Systemic chemotherapy		5 (14.7%)	1 (1.4%)	6 (5.0%)
7. Target therapy		3 (8.8%)	22 (29.7%)	25 (20.8%)
8. Immuno-thrapy		1 (2.9%)	14 (18.9%)	15 (12.5%)
a. Immuno-therapy			14	14
b. Immune-cell therapy		1		1
* Total of methods	12 (10.0%)	34 (28.3%)	74 (61.7%)	120 (100%)

Table 4. Methods of treatment for HCC reported from Taiwan Top-100 articles.

* There were combined two or more methods therapy in an article.

HAI: hepatic arte continuous infusion; PEI: percutaneous ethanol injection; RBRT: external bean radiation; RFA: radio-frequency ablation; RLA: regional local ablation; TAC: transhepatic artery embolization; TACE: transhepatic artery chemo-embolization.

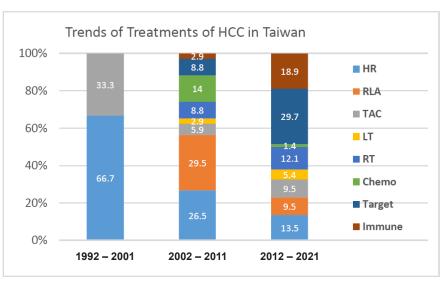


Fig. 3 Trends of treatment methods for the patients of hepatocellular carcinoma during three decades in Taiwan. HR: hepatic resection; RLA: regional local ablation; TAC: trans-hepatic artery chemotherapy; LT: liver transplantation; RT: radiotherapy; Chemo: chemotherapy.

Top-100 articles based on the yearly high-ranking TC listed published from Taiwan. The TC numbers were comparative lower with a mean 10.4, and ranged from 4 to 28 in 2021 due to the short period after publication for citation, but amount of articles was the highest (n = 214)in a single year of 2021. Therefore, we needed to select and to average the representative articles enrolled into Taiwan Top-100 based on the citation number ranking in each year and the amount of publications in each year. In the recent 3rd decade, many published articles concerning the target or immune-therapy with new pharmacologic agents for un-resectable HCC patients were markedly increased. In fact, besides the clinical observation, most of these articles were published on the basic research findings on targeted therapy or immunotherapy with a high rank in this field.¹⁷ Basic research publications usually had a higher citation number than the clinical article in medical science. In Taiwan, due to the new target and immune-therapy were sprung into the list of treatments and accumulated a main topic in the treatment strategies in the 2nd and 3rd decades in Taiwan Top-100.

Surgical resection has been the best choice for HCC patients with a better long

term survival usually.^{18,19} However, surgical resection rates of HCC were recorded 24.79%, 24.86%, 25.81%, and 29.23% for the year 2005, 2010, 2015, and 2019 respectively, according to the report from Ministry of Health and Warfare, Taiwan.1 The positions of liver resections as a study topic including open or laparoscopic approaches were 22.35% totally and decreased by 13.5% in the 3rd decade from Taiwan Top-100 (Table 4). From another study of Xu,¹⁶ the most frequently cited articles that focused on surgical management appeared in the 1980s and decreased after 2010 in the World Top-100. Laparoscopic hepatectomy was started to resect HCC tumor by author Ker CG first in 1998 in Taiwan.²⁰⁻²² Chen PD et al. from National Taiwan University Hospital. began to develop robotic hepatectomy in 2012 and demonstrated less postoperative pain and promising oncological outcomes.²³ Although liver resection has technique demanded, the application in the management algorithm ranks the first if patient matched the practice guideline.^{6-8,24,25}

TACE was primarily choice in one third of HCC patients in the 1st decade. and an alternative non-surgical method with an unsatisfied results usually.²⁶ Besides, the position of preoperative TACE for resectable large HCC was controversy and should be avoided because it does not provide complete necrosis resulting in delayed surgery and difficulties in the surgical treatment.²⁷ Concerning regional local ablation including RFA and percutaneous ethanol injection (PEI) were mentioned in 2004 in Taiwan and the RFA yielded better clinical outcomes than PEI in treating HCC.²⁸ Actually, clinical applications of PEI or RFA were reported early before 1992 in the world

Among Taiwan Top-100, 12 studies concerning radiotherapy were reported and one of these was an international co-operative study of tailoring ⁹⁰Y activity to the clinical circumstances of individual patients as SIRT in 2012.²⁹ Effective treatment can transform a patient with a poor prognosis into a suitable for surgical resection or transplantation with curative intent. In Taiwan, proton beam therapy was applied in the seventy patients of HCC between 2014 and 2017 and their overall survival rates of 6-month, 1-year and 5-year were 100%, 88.4%, 63.4% respectively.³⁰ An international study concerning the proton beam therapy for localized un-resectable HCC and Taiwan was included as a co-author with results of 2-year local control, and overall survival rates were 81% and 62%, with median overall survival was 30.7 months.¹⁵ The articles of proton beam therapy published from Taiwan were 22 articles totally for treatment of HCC and ranking the 5th in the world recorded from Web of Science Core Collection Database searching accessed in July 2022.

Systemic traditional chemotherapy for HCC was not used usually due to the unsatisfied results no matter what agents used.^{31,32} In contrary, molecular targeted agents such as sorafenib were used and clinical results were published in the 2nd decade and become a main topic in the 3rd decade.³³⁻³⁶ Combination of sorafenib with tegafur,³⁷ with everolimus³⁸ or with regorafenib in an international project "RESORCE" trial were reported.³⁹ In addition, sorafenib combined with TACE⁴⁰ or with selective internal radiation therapy in Asia-Pacific patients⁴¹ resulted in selected patients. Among Taiwan Top-100, several clinical trials used target agents included everolimus,⁴² refametinib,⁴³ bevacizumab,⁴⁴ erlotinib,⁴⁵ brivanib^{46,47} linifanib^{48,49} axitinib,⁵⁰ codrituzumab⁵¹ cabozantinib⁵² ramucirumab⁵³⁻⁵⁵ and fisogatinib for the HCC treatment.⁵⁶

Recently, immunotherapy for HCC patients was also a hot issue and nivolumab was the first choice of immune agent for advanced HCC.⁵⁷⁻⁵⁹ An international clinical study in Asia cohort analysis hosted by Yaw in 2019⁶⁰ showed that nivolumab was a safe and effective and being as a treatment option for HCC patients. Two combination with nivolumab and ipilimumab were proved to improve clinical outcome.⁶¹ Another phase I/ II study with tremelimumab plus durvalumab showed it was tolerable in patients but needs further evaluation.⁶² Another four international clinical trials named GO30140 project to treat advanced HCC patients,⁶³ Mbrave 050 project for high risk patients after curative resection or ablation,¹⁴ IMbrave150 project,⁶⁴ and KEYNOTE-240 Trial project in Asia included Taiwan's HCC patients.⁵⁵ The combination of immune agent and targeted agents such as durvalumab with ramucirumab were studied.⁶⁵ In immune cell therapy, dendritic cells (DCs) were the most potent antigen presenting cells and had been applied to treat advanced HCC in 2005 in Taiwan⁶⁶ However, the overall results of current DC vaccination do not yet generate a significant improvement in clinical outcomes.⁶⁷

This was a bibliometric citation analysis to map some information in the trends of interest of study in HCC treatments. The limitations of this study were that an outstanding study might be missing due to the score TC in a comparative year. For example, the most missing of publications from the year 2021 with low TC score (ranged 4 - 28) due to the short time for getting times cited. Hence, some articles were with high TC score and not in the Top-100. Therefore, we have to emphasize the trends and not the solid clinical reality which needs time to prove scientifically always.

In conclusion, the topic of surgical resection for HCC patient was decreased in publication but the trends of clinical choice of treatment were remained in a plateau. On the contrary, molecular targeted agent therapy and immunotherapy were sprung into the main topic of interests concerning the clinical treatment of HCC in the recent decade in Taiwan.

Supplementary Material

eTable 1: List of Taiwan Top-100 articles searching from Web of Science Core Database and selected based on the ranking of times cited in each year published from Taiwan.

Author Contributions

Chen-Guo Ker: design, data collection, identification and writing; Jen-Lung Chen: data collection and check; Yaw-Sen Chen: check and suggestion for completeness.

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Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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