

# Advancements in the study of HCC-MVI: the first bibliometric analysis

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## Research Article

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# Abstract

## Purpose

Over the past decade, several studies have been published regarding the microvascular invasion (MVI) of hepatocellular carcinoma (HCC). However, although these publications have had a remarkable impact on MVI, they have not been quantitatively analysed. Therefore, this study characterised the evolution in HCC-MVI research and systematically evaluated scientific outputs using bibliometric citation analysis.

## Methods

We conducted a systematic search on the Web of Science Core Collection on 2 May 2022 to retrieve studies related to HCC-MVI published between 2013 and 2022. Then, Citespace (v.5.8R3), VOSviewer (v.1.6.18) and other visualisation tools were used to conduct a bibliometric analysis of the publications.

## Results

We identified 1208 articles on MVI in HCC. Of these, while China (n = 518) was the most prolific country, Fudan University (n = 90) was the most notable institution. Furthermore, we observed that while Lau Wan Yee participated in most studies (n = 26), the *Frontiers in Oncology* (IF2020:6.24) published the highest number of documents (n = 49) on this subject, with 138 publications. The paper 'Bray F, 2018, CA-CANCER J CLIN, V68, P394' also presented the highest co-cited references, with 119 citations. Additionally, the top three keywords were 'survival', 'recurrence' and 'microvascular invasion'. Moreover, the research hotspots and frontiers in HCC-MVI for the last three years included 'image' and 'tace'.

## Conclusion

This study comprehensively summarised the most significant HCC-MVI documents from past literature (2013–2022) and highlighted key contributions made to the advancement of this subject and the advancement of this field over the past decade. We propose that this information would provide clinicians and researchers insight into future directions relative to the advancement of HCC-MVI.

## Introduction

As the sixth incident and the fourth leading cause of cancer death among worldwide, the number of new annual cases and deaths from primary liver cancer is now approximately 841 thousand and 782 thousand per year around the world, respectively[1]. Hepatocellular carcinoma (HCC), accounting for 90% of all types in China, is the most common pathological type of liver cancer[2]. Moreover, research has shown microvascular invasion (MVI), only detected by microscopic examination of a surgical specimen, is a major risk factor for tumour recurrence after surgery in HCC[3].

Bibliometric analysis is a quantitative tool, which combines statistical methods with information visualization technology to identify core entities, developmental trends, focusing on specific subjects or research domains. Thus, the technique could offer opportunities to improve the timeliness, accessibility, and reproducibility of literature-based studies during research. Therefore, the method has been widely employed in biomedicine, recently [4]. Specifically, CiteSpace, VOSviewer and R software are the most commonly employed statistical quantitative analysis tools. For example, Xu et al. [5] analysed the 100 most influential articles over the past four decades using VOSviewer and then the R software was used to characterise the evolution in HCC treatment.

Unfortunately, based on our extensive literature search, although several literature-based studies were published on MVI in the past decade, only a few have analysed these published articles using bibliometric citation analysis. Therefore, this study quantitatively evaluated existing scientific outputs to characterise the evolution in HCC-MVI research over the past few years (2013–2022). Subsequently, we propose to provide clinicians and scholars with information that will develop a general understanding of this evolution, facilitating meaningful insight into future directions relative to advances in the HCC-MVI field.

## Materials And Methods

### Literature search and screening

Published literature between 2013 and 2022 was retrieved from the Science Citation Index-Expanded (SCIE) of the Web of Science Core Collection (WoSCC) on 2 May 2022. We conducted all searches on the same day to avoid database update bias, using the following search key terms: Topic = ('primary hepatic cancer') OR ('primary liver cancer') OR ('hepatocellular carcinoma') OR ('malignant hepatoma') OR ('primary liver carcinoma') OR ('primary hepatic carcinoma') AND ('microvascular invasion'). Then, to ensure the representativeness of the included studies, the types of publications were limited to 'article' and 'review'. Meanwhile, this research only included published documents whose language was English. A flowchart of the study is shown in Fig. 1.

### Data analysis and visualisation

Two reviewers (JY Zou and K Sun) were independently identified the raw data, downloaded articles from WoSCC, and excluded duplicate/irrelevant documents. In the case of a discrepancy between the two reviewers, a consensus was reached with the help of a third independent reviewer (T He). Subsequently, CiteSpace (v.5.8 R3) was adopted as the search tool to analyse institutions, co-cited references and keywords. And the VOSviewer (v.1.6.18) was used to analyse authors, co-cited authors and journals. Finally, after Excel 2019 showed a trend in the number of articles published by year, we created a world map of the publications' number and country's cooperation using ECharts (v.4.5.0) and SCImago Graphica Beta (v.1.0.18), respectively.

# Results

Our investigation revealed that 6799 authors who completed 1208 manuscripts in this study were from 1088 institutions in 41 countries, of which articles and reviews were 1101 and 107, respectively. Moreover, they were published in 297 journals, citing 22,505 references from 2,673 journals.

## Annual outputs

The annual publications showed an obvious upward trend during the period under review (2013–2022) (Fig. 2). Furthermore, investigations revealed that the average annual output was approximately 120 documents, with 2021 being the year with the most publications.

## Countries and institutions

Among the manuscripts from 41 countries (Fig. 3.) identified, China (including Hong Kong, Macau and Taiwan) participated in most studies ( $n = 518$ ), accounting for 42.88% of all documents, followed by South Korea (136), the US (125) and Japan (101). Figure 4 depicts the partnership among countries that published these articles, demonstrating cooperation among the various countries. Notably, China had the strongest cooperative relations with the US in this field. Meanwhile, 1088 institutions contributed to MVI research. The partnerships between the institutions actively carrying out research are illustrated in Fig. 5. As shown, the top three institutions that published the most articles included Fudan University (90 documents), the Second Military Medical University (83 documents) and the Sichuan University (78 documents), with 1442, 1708 and 1139 total citations (TCs), respectively. However, the Chinese University of Hong Kong ranked first based on average citations ( $n = 30.35$ ).

## Authors and co-cited authors

With more than 6000 authors, the knowledge map provided the information regarding the most influential authors including their collaborative relationships (Fig. 6). Investigations revealed that among the top 10 contributive authors (Table 2), Lau Wan Yee and Li Bo were the most productive authors, each with 26 publications, followed by Shen Feng with 22 publications. As a co-cited author, Bruix J (499 citations) was ranked first, followed by Llovet JM (454 citations) and Mazzaferro V (443 citations).

Table 1  
The top 10 institutions contributed to publications in the HCC-MVI research

Rank	Institution	country	counts	TCs	Average TCs
1	Fudan University	China	90	1442	16.02
2	Second Military Medical University	China	83	1708	20.57
3	Sichuan University	China	78	1139	14.60
4	Sun Yat Sen University	China	74	1065	14.39
5	Sungkyunkwan University	Korea	49	883	18.02
6	The Chinese University of Hong Kong	China	37	1123	30.35
7	Fujian Medical University	China	36	273	7.58
8	Guangxi Medical University	China	35	434	12.40
9	Southern Medical University	China	29	455	15.68
10	Zhejiang University	China	28	310	11.07

Table 2  
The top 10 authors and co-cited authors in the HCC-MVI research

Rank	Author	Counts	Co-cited Author	counts
1	Lau wan yee	26	Bruix J	499
2	Li bo	26	Llovet jm	454
3	Shen feng	25	Mazzaferro V	443
4	Li chuan	22	Poon rtp	304
5	Joh jae-won	22	Roayaie S	295
6	Kim jong man	21	Rodriguez-peralvarez m	276
7	Zhou jian	20	Forner A	246
8	Wu mengchao	18	Sumie S	243
9	Fan jia	17	Lim KC	233
10	Li jun	17	European assoc study liver	207

Active journals

The results shown that 297 journals participated in this field. Table 3 lists the number of articles published, the top 10 journals, their TCs, impact factors (IFs) 2020 and Journal Citation Report (JCR) areas. Accordingly, while *Frontiers in Oncology* published 49 documents and ranked first over the past decade, the journal that had the highest number of citations was *Annals of Surgical Oncology*, with 1014 TCs. Furthermore, the IF of journals, excluding *Oncotarget*, ranked from 1.89 (*Medicine*) to 6.24 (*Frontiers in Oncology*), with an average IF of 4.34. Simultaneously, approximately 70% of the top 10 journals scored Q1/Q2 in the JCR partition. Recently, *Frontiers in Oncology* and *European radiology* have been the hottest journals in the field (Fig. 7). As shown in Fig. 8, the two green citation paths indicated that journals published in molecular/biology/genetics and health/nursing/medicine were also cited by medicine and medical/clinical journals.

Table 3  
The top 10 journals contributed to publications in the HCC-MVI research

Rank	Journal	Counts	TCs	IF2020	JCR area
1	Frontiers in Oncology	49	138	6.24	Q2
2	Medicine	40	319	1.89	Q3
3	European Radiology	32	607	5.32	Q1
4	Annals of Surgical Oncology	30	1014	5.34	Q1
5	Oncotarget	29	670	NA	NA
6	Journal of Gastrointestinal Surgery	23	332	3.45	Q2
7	HPB	22	457	3.65	Q1
8	World Journal of Gastroenterology	21	732	5.74	Q2
9	Bmc Cancer	21	447	4.43	Q3
10	Abdominal Radiology	20	217	3.04	Q2

## References analyses

We adopted Citespace to characterise the relationship between co-cited references based on the retrieved literature. As shown in Fig. 9, while the largest cluster was '#0 radiomics', '#0 radiomics', and '#4 metabolic dysfunction-associated fatty liver disease' have developed into the hottest research topics over the past two years. We also analysed the top 10 co-cited references in the Table 4. Of the 1208 manuscripts shown, three articles were cited more than 100 times. Moreover, the articles published by Bray F et al. in 2018 ranked first with 119 citations, followed by that by Lei Z, with 117 citations.

Table 4  
The top 10 co-cited references in the HCC-MVI research

Rank	Co-cited Reference	Counts
1	Bray F, 2018, CA-CANCER J CLIN, V68, P394	119
2	Lei Z, 2016, JAMA SURG, V151, P356	117
3	Lee S, 2017, J HEPATOL, V67, P526	114
4	Renzulli M, 2016, RADIOLOGY, V279, P432	96
5	Xu X, 2019, J HEPATOL, V70, P1133	79
6	Torre LA, 2015, CA-CANCER J CLIN, V65, P87	78
7	Rodriguez-Peralvarez M, 2013, ANN SURG ONCOL, V20, P325	74
8	European Assoc Study Liver, 2018, J HEPATOL, V69, P182	71
9	Cong WM, 2016, WORLD J GASTROENTERO, V22, P9279	65
10	Fornier A, 2018, LANCET, V391, P1301	63

### Keywords and burst keywords

We also analysed the active keywords mentioned most frequently and the timeline view of these studies (Fig. 10). Statistics data showed 'survival', followed by 'recurrence' and 'microvascular invasion', as the keywords with the highest frequency. Furthermore, of the 17 keywords with the strongest citation bursts (Fig. 11), the 'Milan criteria' had the strongest citation burst of 5.39. Recently, "image" and "tace" became the focus in this field.

## Discussion

### General information

Based on our extensive literature search, this is the first comprehensive and quantitative analysis to provide a systematic research data on the literature related to HCC-MVI. This research provides a wide and visual analysis of publications in this field, which may help scholars gain a basic understanding, develop areas of focus, identify trends and pursue further practise in this field.

The top 10 countries that published articles in this field included three Asian countries, five European countries and two American countries, accounting for 62.5%,14.81%,11.67% of all documents, respectively .Furthermore, our investigation revealed that more than 40 percent of the countries had more than 100 publications. China, the only developing country in the top 10,also contributed more than 40% of documents,indicating its high academic impact on the HCC-MVI field.However, although they cooperated extensively with other countries, especially the US, their global cooperation was not strong enough (e.g.

with Europe). Besides this, another remarkable phenomenon was that nine Chinese universities were among the top 10 institutions that contributed to publications, showing the dominant position of Chinese researchers in this field. Additionally, the incidence of HCC in Asia was higher than in Europe and America[1], which may be why China had the most prolific research on this topic.

#### Citation information

Notably (Table 2), all of the top 10 active authors published at least 17 articles. In the list, however, although eight of the ten leading contributors were Chinese, which was consistent with the results of institutional research, none of them were reflected in the top 10 co-cited authors who generated high-quality articles and were more influential. As the highest co-cited author, Bruix J (the Barcelona Clinic Liver Cancer Group, University of Barcelona, Spain) contributed extensively to developing HCC management guidelines[6], and completed numerous of high-quality studies[7–9]. Meanwhile, Llovet JM and Mazzaferro V made notable contributions to the HCC field[10–12].

Based on academic journals (Table 3), although the retrieved ones in this field were not high-impact factor journals, *Frontiers in Oncology* had the highest IF and published the highest number of articles. Nevertheless, they received the lowest number of citations in the top 10. Our study also revealed that although *Annals of Surgical Oncology*, published original and educational manuscripts on oncology for surgeons from all specialities in academic and community settings, they merely ranked 4th, and then got the highest number of citations. The clear difference between the two journals might be related to the lower open-access articles. Remarkably, however, since 2020, the number of articles published by *Frontiers in Oncology* and *European Radiology* increased substantially. Based on co-cited references, as the head of the international agency for research on cancer, Bray F, who was not a highly co-cited author (Table 2), comprehensively described the epidemiological characteristics of malignancy[1], and had the highest number of co-citations in 2018. On the other hand, we observed that the Chinese published only three documents (Table 4). As a Chinese author with the most cited references, Lei Z, published a paper on ‘nomogram for preoperative estimation of microvascular invasion risk in hepatitis b virus-related hepatocellular carcinoma within the Milan criteria’, which elaborated how to construct a nomogram using clinical and imaging information and achieved an optimal preoperative prediction of MVI in HBV-related HCC within the Milan criteria[13]. What is noteworthy is that the document, only ranked 6th in the top 10 co-cited references, written by an accomplished medical epidemiologist, Torre LA, and published in the journal of *Ca-A Cancer Journal for Clinicians*, with the highest IF 508 in academia[14]. Simultaneously, while this study was the most cited from a Q1 journal, it was mainly a review based on a WoS ranking, which may be why it has been so widely cited over the past decade.

#### Research hotspots and frontiers

Keywords and burst keywords (Figs. 10 and 11) reflect the research’s focus. A decade ago, several scholars described how to predict MVI and interpret its effects based on prognosis. For example, Shirabe et al. [15] revealed tumour size, serum des-gamma-carboxy prothrombin (DCP) levels and the maximum standardised uptake value (SUVmax) on 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography

were independent clinical predictors of MVI after multivariate analyses. The doctors and radiologists at the centre for imaging science of Sungkyunkwan university, also combined two or more of the following, arterial peritumoral enhancement, a non-smooth tumour margin, and peritumoral hypointensity at the hepatobiliary phase, as preoperative imaging biomarkers to predict MVI through gadoteric acid-enhanced magnetic resonance imaging. These biomarkers which are associated with early recurrence after curative resection of single HCC [16]. Zhao et al. [17] constructed a scoring system based on AFP/SGPT level, tumour diameters and tumour number. Their results indicated when the score was greater than 3, the incidence of MVI increased by five times, whereas the overall survival rate decreased significantly. Meanwhile, the "Milan criteria", which had the strongest citation burst (5.39), was the focus of the field from 2013 to 2018. Furthermore, several clinicians deemed MVI was one of the independent risk factors for tumour recurrence in HCC, classified within the Milan criteria [18]. Moreover, research on similar articles showed a rapid growth trend, which may have accounted for the frequent keywords 'survival', 'recurrence', 'risk factor' and 'Milan criteria'. We also observed that 'gamma carboxy prothrombin', also termed Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II), was associated with early recurrence after curative resection of a single HCC and has been extensively applied in the MVI field [19].

Burst keywords refer to those widely cited in articles within a particular period, which are considered another significant indicator of research hot spots or emerging trends. For example, as shown in Fig. 11, research hotspots and frontiers in the MVI included 'image' and 'tace' within the last three years.

1. Image: An important issue affecting HCC prognosis is the absence of a highly reliable factor to predict MVI preoperatively. Thus, several image radiomics studies have been incorporated into the MVI report. For example, Jiang et al. [20] developed predictive models using Xtreme Gradient Boosting (XGBoost) and deep learning based on computerised tomography images to predict MVI preoperatively. However, Li et al. [21] verified through the promising technique of magnetic resonance elastography-based shear strain mapping that the low interface shear strain identified at tumour-liver boundaries was highly correlated with the presence of MVI. Except that, scholars have evaluated the maximum standardised uptake value (SUVmax) of preoperative fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography (F-FDG PET-CT), and summarised the combination of the two risk factors (SUVmax and AFP-L3), providing a reliable assessment for predicting MVI, with the sensitivity and specificity of 88.9% and 82.4%, respectively [22]. In addition to this finding, based on a retrospective study, Xu et al. [23] developed a computational approach integrated 15 clinical factors, and 12 imaging features from contrast-enhanced CT. Their study demonstrated good performance in predicting MVI and clinical outcomes, using multivariate logistic regression.

2. transarterial chemoembolization (TACE): As one of the important non-surgical treatment methods for HCC, TACE can reduce tumour recurrence rates and increase the overall survival rates, especially in patient in advanced stages [2, 24]. The controversial focus of these studies was to investigate whether postoperative-TACE (p-TACE) improved the prognosis of patients with MVI. For example, Yang et al. [25] included 13 studies in which 824 patients received p-TACE, which significantly improved overall survival (OS) and recurrence-free survivals (RFS) compared with postoperative conservative treatment in

patients with HCC accompanied by MVI after curative resection. Similarly, Li et al. [26] considered p-TACE as a safe intervention which reduced tumour recurrence rates and improved the OS for MVI using high-quality meta-analysis. Besides, the recent results showed that only patients with BCLC stage A, CNLC stage Ib, and AJCC stage II both were found to be benefited more from p-TACE, but not patients with BCLC stage 0/B, CNLC stage IIb, and AJCC stage IIIa [27]. Contrastingly, they declared that p-TACE was not inferior to more cycles when improving prognosis, strongly recommending only one cycle following R0 resection [27, 28].

### Research strengths and limitations

To our knowledge, this study is the first to systematically research the literature related to HCC-MVI. Our study also provided a comprehensive and quantitative analysis of the most significant MVI articles, acknowledging the key contributions made to the evolution and advancement of this specialised field. However, we encountered some limitations. First, the data analysed in the study were only from WoSCC-SCIE, which excluded other databases, such as PubMed, Scopus and Embase. Moreover, we partially selected documents (articles and reviews) and defined the focus language as English, resulting in some linguistic bias. Therefore, since data are typically prone to frequent changes, our results only reflected the current state of HCC-MVI research. Hence, data generated from studies published in the current year (2022) were incomplete in our analysis. Finally, self-citations are a significant problem that can influence these results.

## Conclusions

This bibliometric study identified a continual increase in MVI-related studies from 2013 to 2022, with China leading the field. Additionally, the themes 'image' and 'tace' were the most recent research topics. Therefore, researchers should devote additional attention to these topics.

## Abbreviations

HCC Hepatocellular carcinoma

MVI Microvascular invasion

SCIE Science citation index-expanded

WoSCC Web of science core collection

IF Impact factor

JCR Journal citation report

DGP Des-gamma-carboxy prothrombin

TCs Total citations

PIVKA-II Protein induced by vitamin k absence or antagonist-II

SUV Standardised uptake value

TACE Transarterial chemoembolization

## Declarations

Conflict of interest

The authors declare that they have no competing interests.

Ethics statement

We performed statistical analysis based on the WoSCC database, and the ethical requirement wasn't required for this research.

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Author Contributions

TH and JZ: article writing. TH, JZ, LX, TL and SY: performed image acquisition. TH, JZ and KS: data collection. TH, JZ, SY, LX, TL, JY and GL: revised and improved the manuscript.

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## Figures

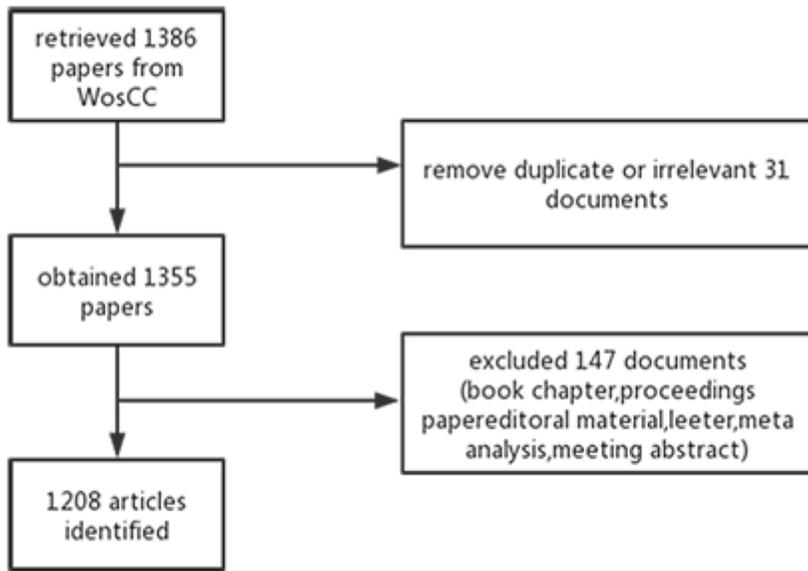


Figure 1

A flowchart of the study to retrieve HCC-MVI articles from the WosCC database.

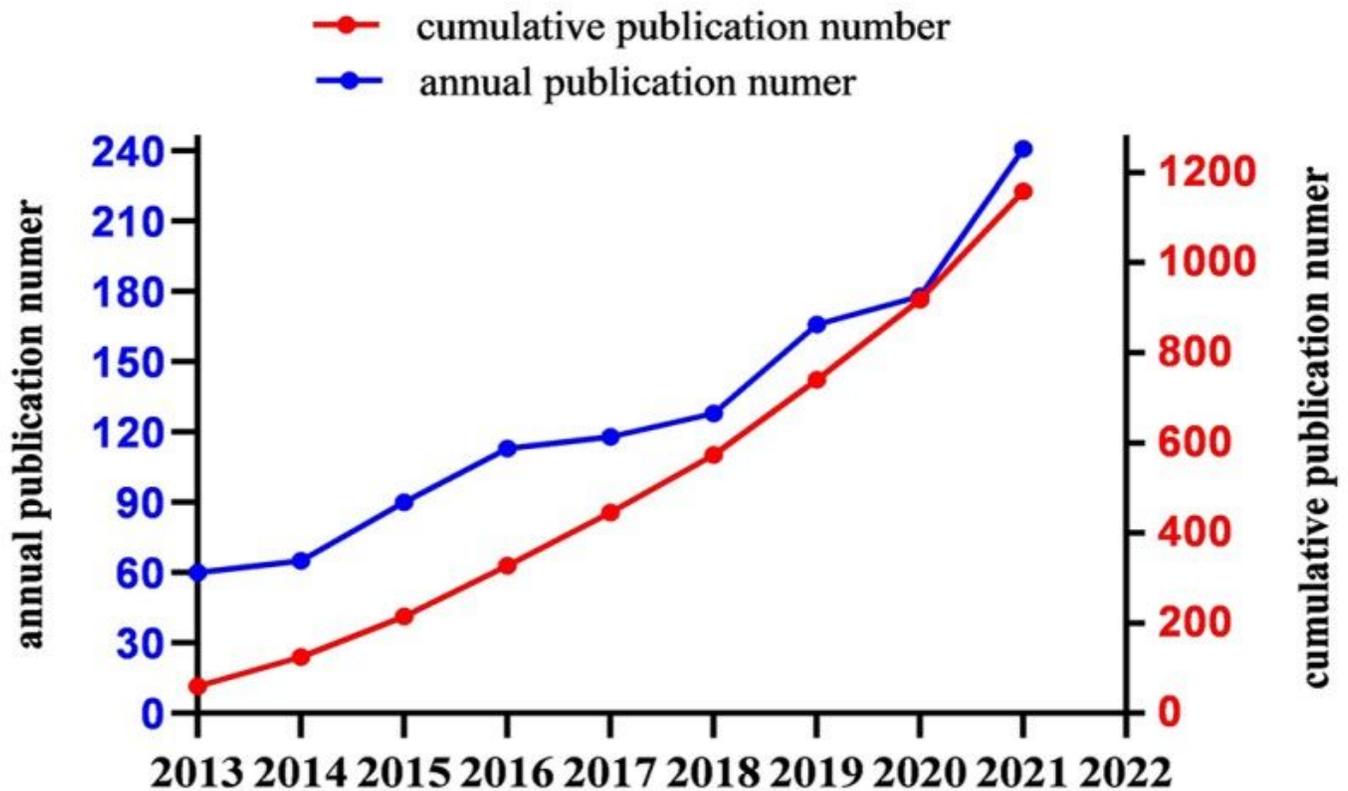
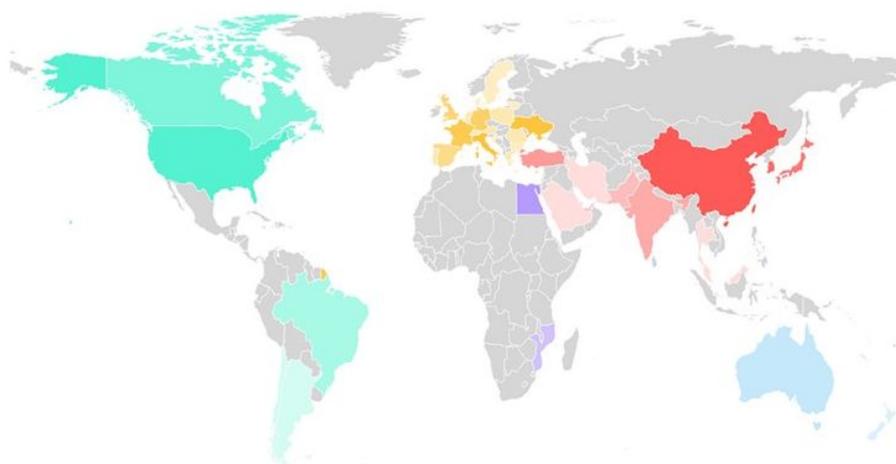


Figure 2

Number of publications by year.



**Asia**

- China(518)
- Korea(136)
- Japan(101)
- Singapore(10)
- Turkey(8)
- India(4)
- Pakistan(4)
- United Arab Emirates(2)
- Iran(1)
- Malaysia(1)
- Saudi Arabia(1)
- Thailand(1)

**Americas**

- United States(125)
- Canada(16)
- Brazil(9)
- Argentina(2)
- Chile(1)

**Europe**

- Italy(63)
- France(54)
- Germany(25)
- United Kingdom(19)
- Spain(18)
- Austria(8)
- Belgium(9)
- Netherlands(8)
- Portugal(7)
- Poland(6)
- Romania(6)
- Switzerland(6)
- Greece(5)
- Croatia(2)
- Denmark(2)
- Sweden(2)
- Bulgaria(1)
- Lithuania(1)
- Scotland(1)

**Australia**

- Australia(14)
- New Zealand(1)

**Africa**

- Egypt(8)
- Mozambique(1)



**Figure 3**

Number of publications by country.



**Figure 4**

The network map of countries cooperation.(The size of the node represented the number of publications, and the color of the line shown the strength of cooperation)

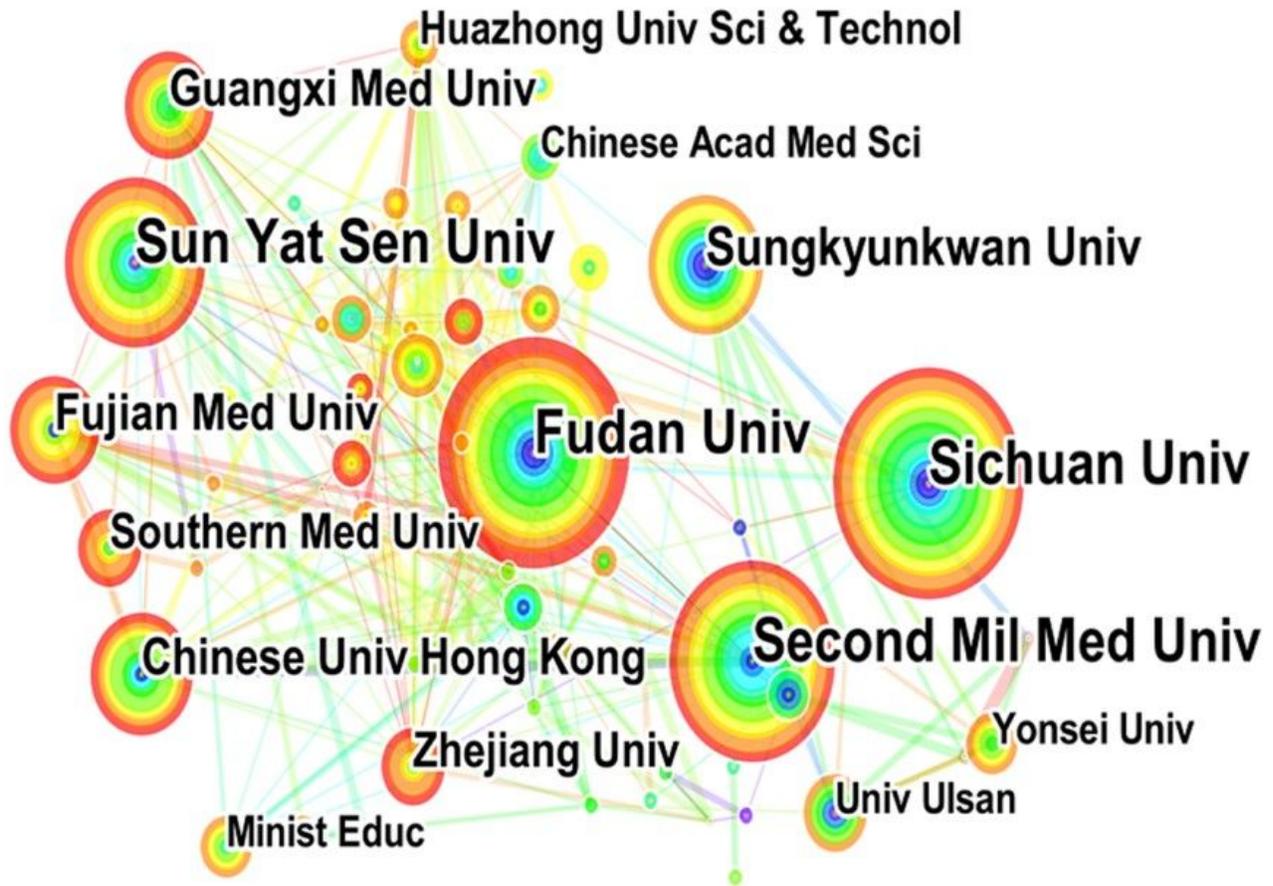


Figure 5

The bibliometric analysis of active institutions in the HCC-MVI research.

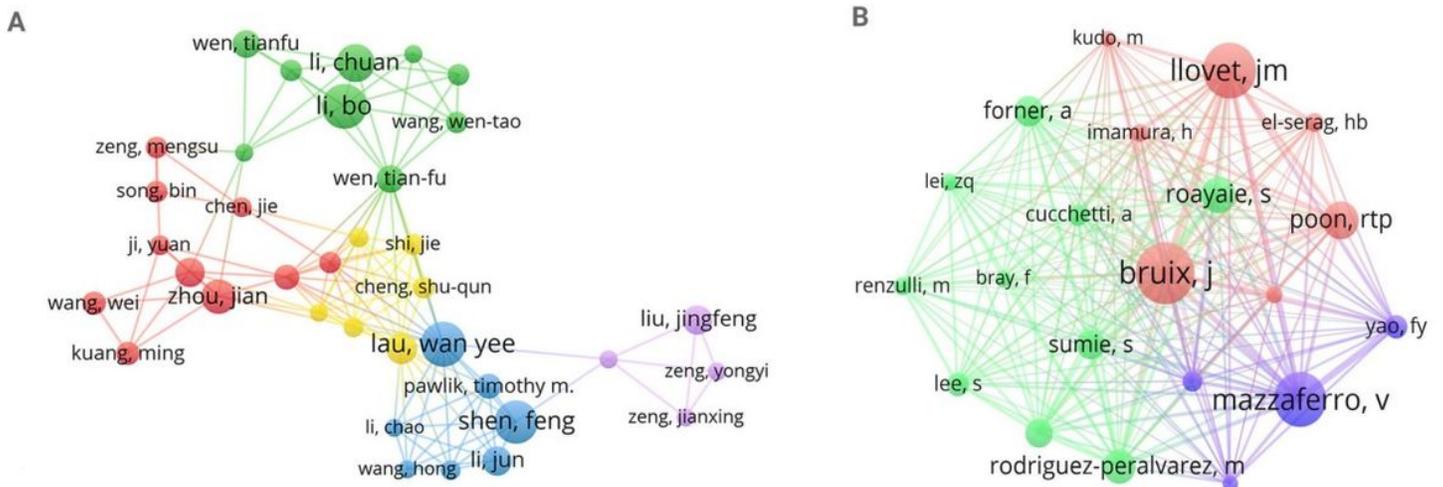
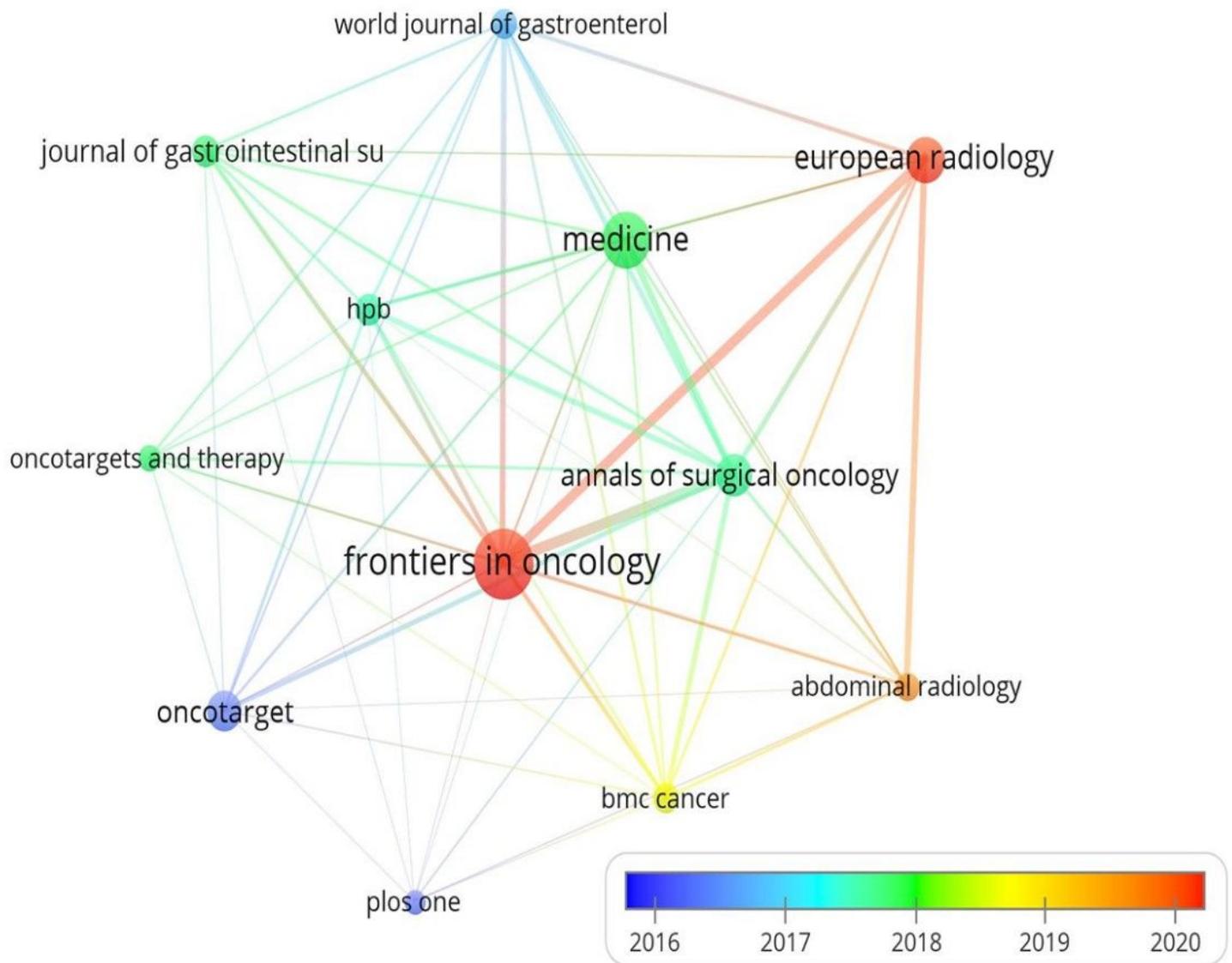


Figure 6

The knowledge map of active authors and co-cited authors in the HCC-MVI research.(A. active authors. B. active co-cited authors)



**Figure 7**

The bibliometric analysis of active journals in the HCC-MVI research.

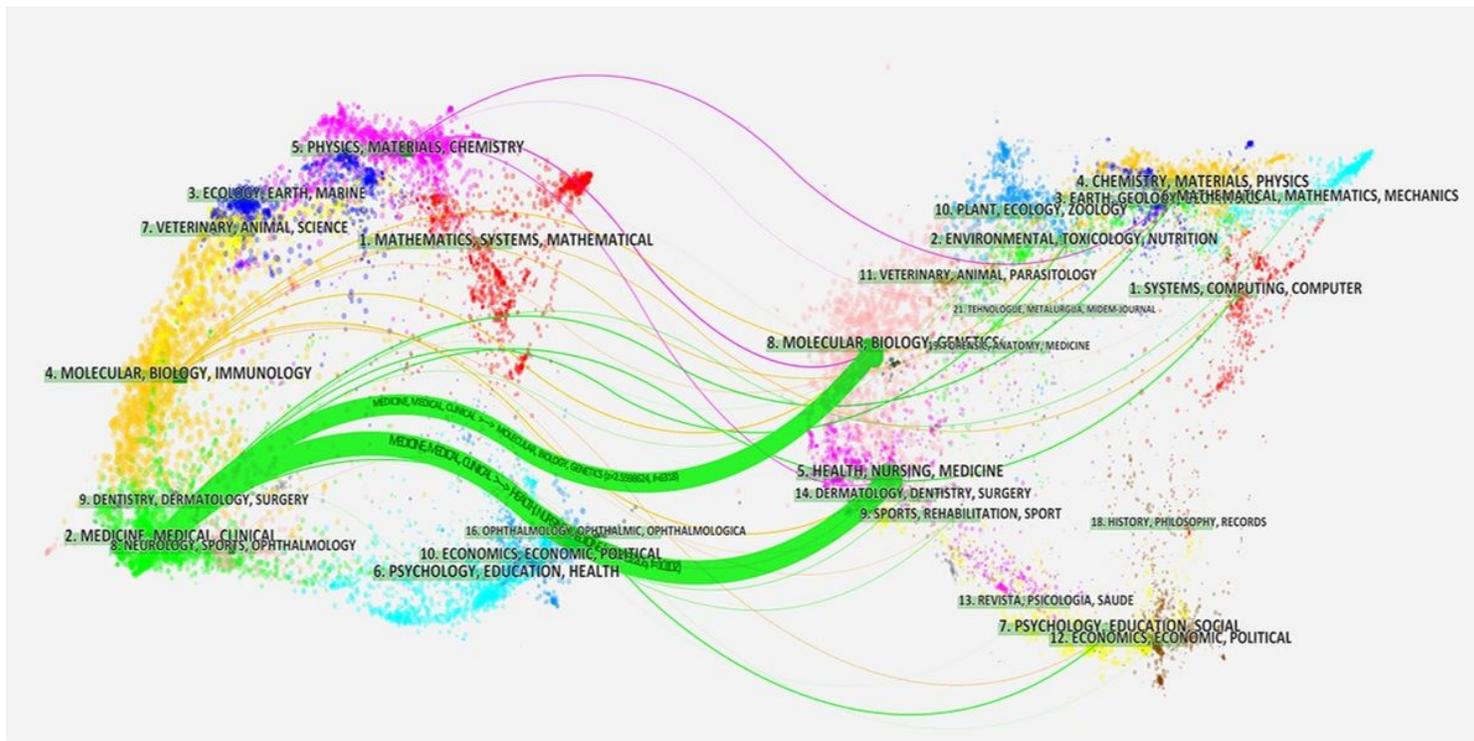


Figure 8

The dual map overlay of journals in the HCC-MVI field.(left:citing journals; right:cited journals)

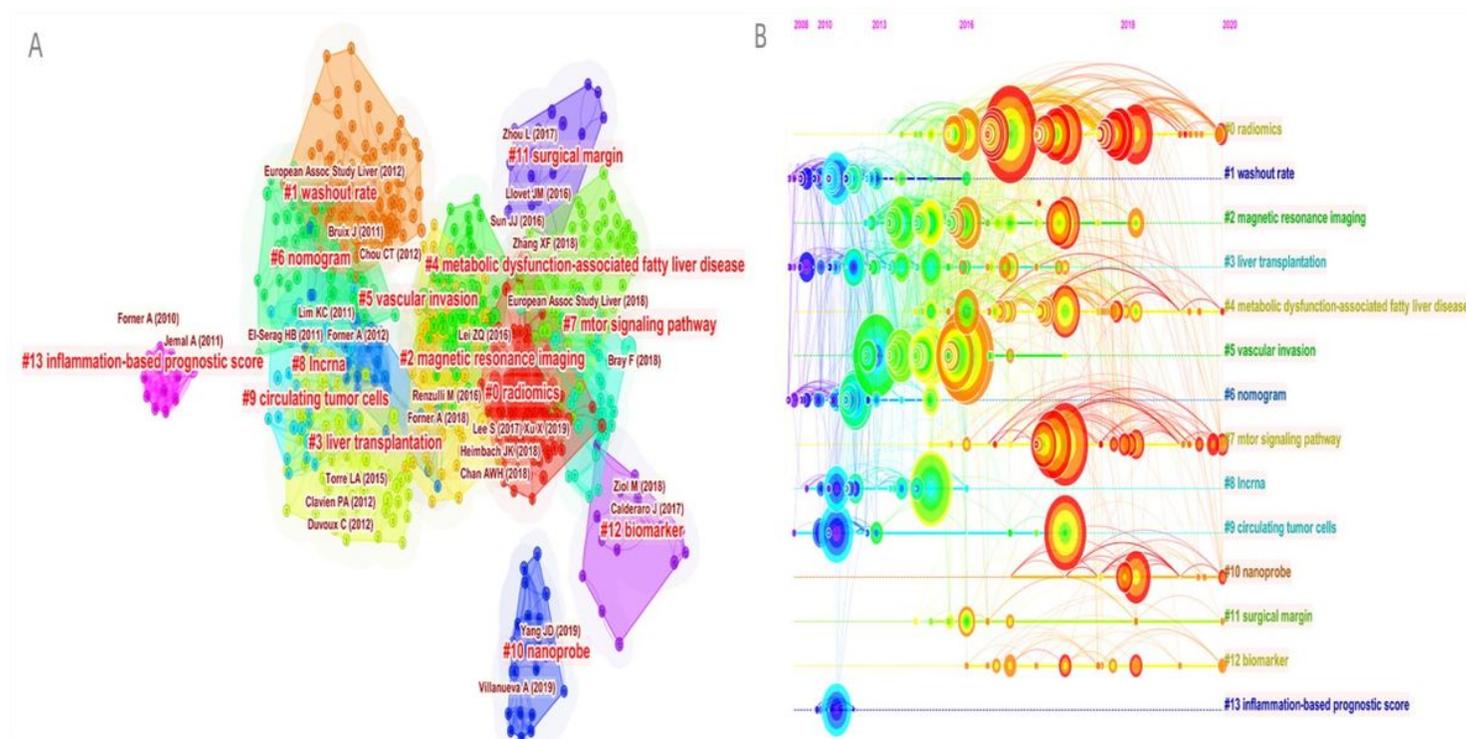


Figure 9

The cluster view and timeline view of co-cited references in the HCC-MVI research.(A: cluster view; B: timeline view)

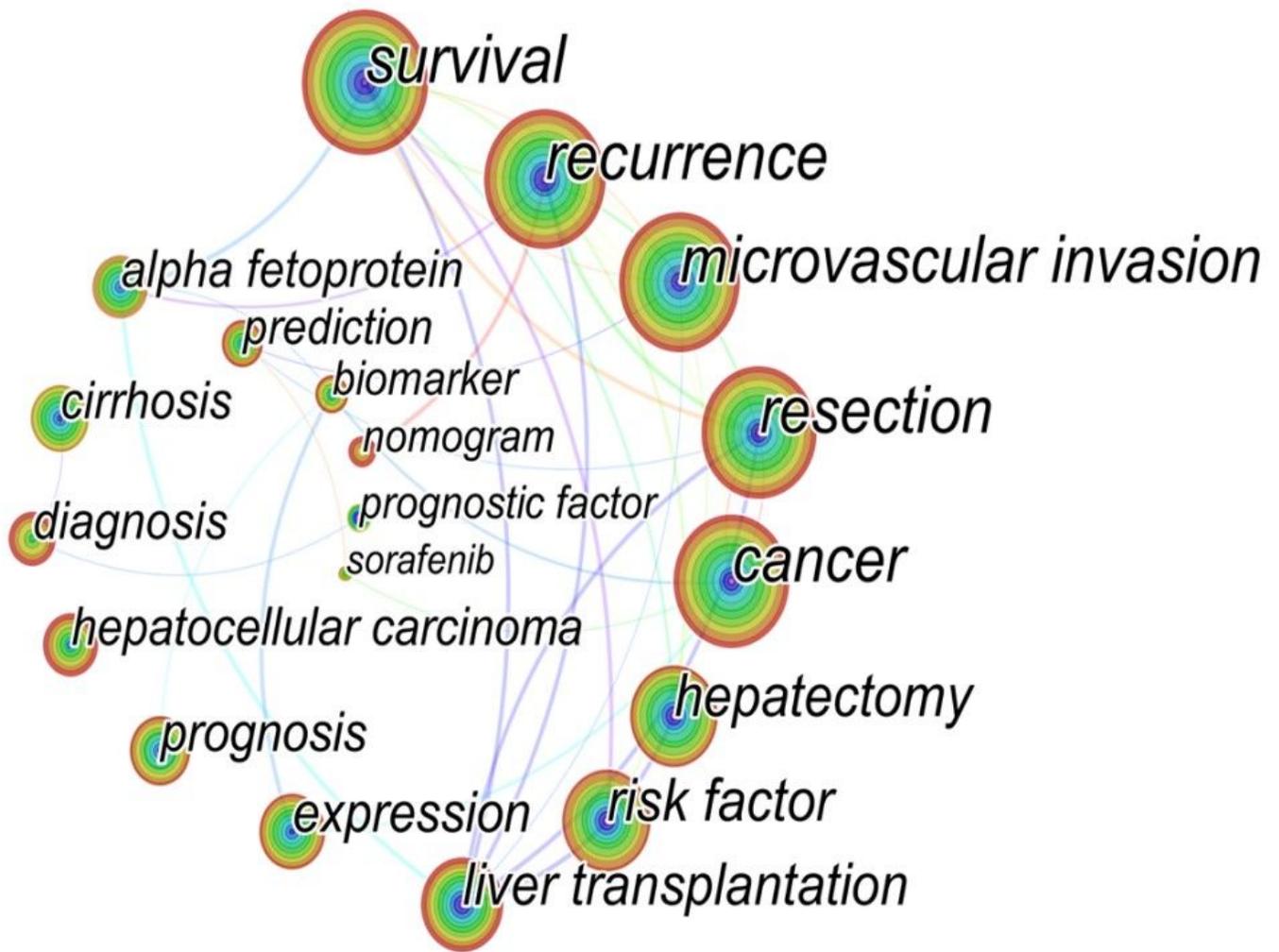


Figure 10

The map of active keywords in the HCC-MVI research.

# Top 17 Keywords with the Strongest Citation Bursts

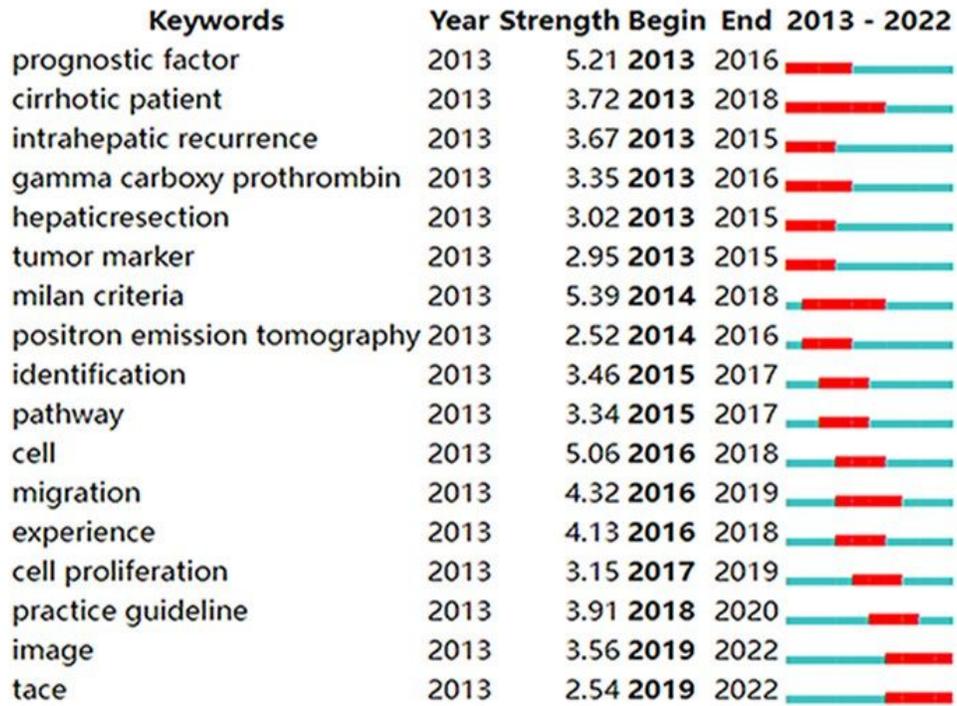


Figure 11

The keywords with the strongest citation bursts from 2013 to 2022 in the HCC-MVI research.