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Insights into the history and tendency of liver transplantation for liver cancer: a bibliometric-based visual analysis

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Abstract

Research on liver transplantation (LT) for liver cancer has gained increasing attention. This paper has comprehensively described the current status, hotspots and trends in this field. A total of 2991 relevant articles from 1 January 1963 to 28 February 2023 were obtained from the Web of Science Core Collection. VOSviewer and CiteSpace software were utilized as bibliometric tools to analyze and visualize knowledge mapping. Between 1963 and 2023, the number of papers in the area of LT for liver cancer increased continuously. A total of 70 countries/regions, 2303 institutions and 14 840 researchers have published research articles, with the United States and China being the two most productive countries. Our bibliometric-based visual analysis revealed the expansion of LT indications for liver cancer and the prevention/treatment of cancer recurrence as ongoing research hotspots over the past decades. Meanwhile, emerging studies also focus on downstaging/bridging treatments before LT and the long-term survival of LT recipient, in particular the precise application of immunosuppressants.

Keywords: bibliometrics, liver cancer, liver transplantation, visualization

Introduction

Since the first liver transplantation (LT) was executed by Dr. Thomas E. Starzl in 1963[1], past decades have witnessed rapid progress in LT, especially with the application of effective immunosuppressants and developments in surgical techniques and perioperative management. Nowadays, LT has already been well-recognized as the only curative method for end-stage liver diseases, including but not limited to liver cancer, liver failure, and inborn metabolic diseases[2–4]. According to the Organ Procurement and Transplantation Network (OPTN) database, 9234 LTs were performed in the United States in 2021[5].

As Dr. Thomas E. Starzl stated, the unequivocal indication for LT was originally considered to be hepatic malignancy, which could not be treated with liver resection[6]. Liver cancer consists of primary and secondary liver malignancies and is the leading cause of cancer death. For primary liver cancer, hepatocellular carcinoma (HCC) is the predominant pathological type[7], and the majority of HCC occurs on a background of cirrhosis. LT not only serves as a curative treatment against multiple tumor burdens, but also replaces a cirrhotic liver, thus considerably improving the prognosis of HCC patients. Several retrospective studies have revealed that 5-year overall survival (OS) of HCC patients after LT was significantly higher (59.3 to 89.0%) than liver resection (41.0 to 76.0%), indicating LT as a favorable choice against HCC[8–10]. As estimated, LT for HCC accounts for

HIGHLIGHTS

- This study presents the first bibliometric analysis in the field of liver transplantation (LT) for liver cancer, with the United States and China as the two most productive countries.
- The number of papers in the field of LT for liver cancer was increasing steadily from 1963 to 2023.
- The expansion of LT indications for liver cancer and the prevention/treatment of cancer recurrence were the ongoing research hotspots.
- Emerging studies also focus on downstaging/bridging treatments before LT and the long-term survival of LT recipient, especially the precise application of immunosuppressants.

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about one-third in most LT centers worldwide[11]. Clinical researches also indicated LT as an effective therapeutics against the remaining two primary liver cancers, including intrahepatic cholangiocarcinoma (ICC), and combined HCC and intrahepatic cholangiocarcinoma (cHCC-ICC)[12,13]. Secondary liver malignancies, also named liver metastases, are more common than the primary ones. Almost all solid malignancies could metastasize to the liver, further causing multiple liver tumor lesions without specific clinical symptoms. Recent clinical trials also have shown a promising role of LT in the therapeutics against liver metastases, especially for the unresectable ones[14–17]. Taken colorectal liver metastases (CRLM) for an example, SECA-I study, performed by the Norwegian group, enrolled 21 patients who underwent LT for nonresectable colorectal liver metastases (NRCLM) and the 5-year OS was 60.0%[18].

Currently, numerous studies have been published in LT for liver cancer. Bibliometrics is the quantitative analysis of a mass of literature in a particular field of research using mathematical and statistical methods combined with visualization tools to reveal numerous aspects and trends in the evolution of a scientific subject[19]. Bibliometrics studies have already been used in various aspects for systematically assessing publications in a certain field of study[20,21]. Herein, we obtained a total of 2991 relevant articles in LT for liver cancer from 1963 to 2023 in the Web of Science Core Collection. VOSviewer and CiteSpace software were utilized as bibliometric tools to analyze and visualize knowledge mapping. Hence, we intended to show the development of LT for liver cancer and state-of-the-art hotspots, further guiding clinical and basic researches.

Method

Data collection

The Web of Science Core Collection (WOSCC) was selected as the primary database of our study. We searched articles of LT for liver cancer published between 1 January 1963 and 28 February 2023 with the following formula: (TI = (Liver Neoplasm) OR TI = (Hepatic Neoplasm) OR TI = (Liver Cancer) OR TI = (Hepatic Cancer) OR TI = (Liver tumor) OR TI = (Hepatic tumor) OR TI = (Hepatocellular Cancer) OR TI = (Hepatocellular Carcinoma) OR TI = (HCC) OR TI = (Hepatoma) OR TI = (Liver malignancy) OR TI = (liver malignant tumor) OR TI = (ICC) OR TI = (Cholangiocarcinoma) OR TI = (Intrahepatic cholangiocarcinoma) OR TI = (Liver Metastasis) OR TI = (neuroendocrine tumor) OR TI = (Angiosarcoma)) AND (TI = (LT*) OR TI = (Grafting, Liver) OR TI = (Liver Grafting) OR TI = (Transplantation, Liver) OR TI = (Liver Transplant*) OR TI = (Transplant, Liver) OR TI = (Hepatic Transplantation*) OR TI = (Transplantation, Hepatic)). The entire WOSCC records including the cited references were downloaded in TEXT format within 1 day of 20 March 2023 to minimize possible deviations caused by database updates. The flowchart of data collection and analysis was illustrated in Figure 1A.

Data analysis

The bibliometric tools used in this paper were VOSviewer (version 1.6.18) and CiteSpace (version 6.2.R2 Advanced). VOSviewer, a visualization software developed by Leiden University[22], was used to conduct collaborative network analysis of countries, institutions, and authors, as well as co-occurrence network and density analysis of keywords. CiteSpace is a widely-used software for visual analysis[23] and could provide co-citation analysis and citation bursts analysis, supporting the identification of research trends and hotspots in the field. Pajek provided assistance to modify the layout of the cluster map.

Results

Annual publications and citations

A total of 2991 papers were included, and annual publications and citations were counted. The statistics for the number of articles published in 2023 are incomplete due to the retrieval time. As shown in Figure 1B, both the number of publications and citations increased steadily, with a rapid increase after 2000. The number of publications and citations in 2021 reached 210 and 7733, respectively. The sharp increase after 2000 reflected the widespread application of LT techniques and the focus of academics in general.

Analysis of cooperation status

Countries/regions

A total of 70 countries contributed to the research of LT for liver cancer. The most productive country/region was the United States ($n=826$, 27.62%), followed by China ($n=428$, 14.31%), Italy ($n=267$, 8.93%), Germany ($n=246$, 8.22%), and Japan ($n=218$, 7.29%) (Fig. 2A). The top 10 countries, including five European countries, three Asian countries and two North American countries, have published 2784 papers, accounting for 93.08% of the total papers published. Figure 2B displayed the extensive cooperation between the thirty most productive countries/regions. As a whole, countries with a significant number of publications also collaborated more, with the United States the most notable.

Institutions

LT for liver cancer was conducted at ~2303 institutions worldwide, with the top 10 institutions in terms of literature output and their number of citations were shown in Table 1. Assistance Publique Hopitaux Paris (APHP) had the most significant number of publications ($n=130$, 4.35%) followed by UDICE French Research Universities ($n=114$, 3.81%). Primary institutions and their collaborative relationships in this field of were illustrated in Figure 2C. The co-occurrence analysis of institutions observed that the institutions with great number of publications generally have close collaborative relationships with each other and domestic cooperation is more common than international cooperation.

Authors

More than 14 000 researchers participated in research about LT for liver cancer. Zheng Shusen ($n=69$) from China was the author with the most publications, following with Cillo Umberto ($n=51$), and Lee Sung-Gyu ($n=49$) as well as Mazzaferro Vincenzo ($n=49$) (Table 2). The author co-occurrence analysis indicated the several research groups and cooperation between researchers in this field (Fig. 2D). The node size was positively correlated with the number of

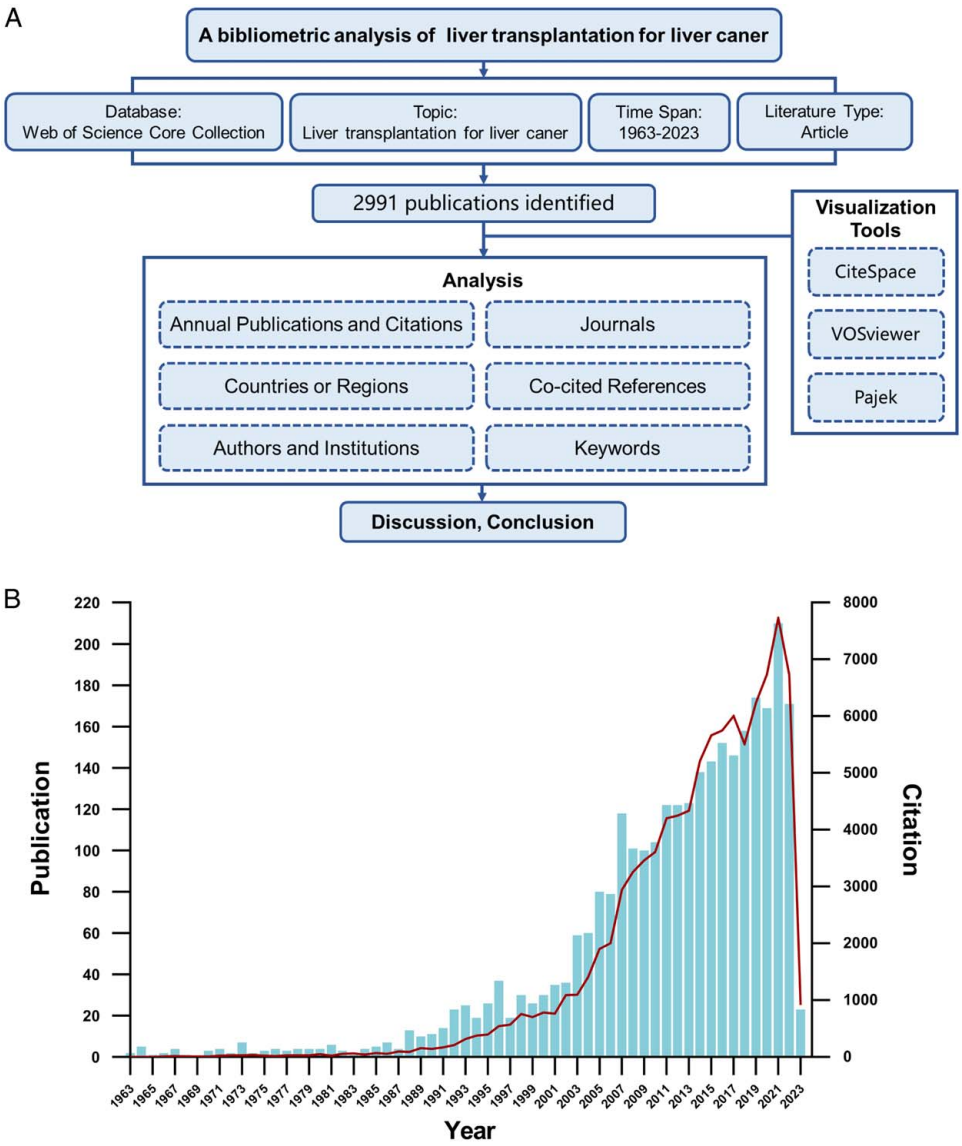

Figure 1. (A) Flowchart of bibliometric analysis. (B) The number of articles about liver transplantation for liver cancer per year from 1963 to 2023.

publications of a certain author and line thickness between nodes represented the cooperation frequency.

Analysis of journals

Up to March 2023, 531 SCI journals have published articles in the field of LT for liver cancer. The top 10 journals with the most publication quantity sorted by total citations were summarized in Table 3, accounting for 39.08% of the whole. TRANSPLANTATION PROCEEDINGS was the most published journal ($n = 415$, 13.88%) and LIVER TRANSPLANTATION was the most cited one (citations = 13 814). ANNALS OF SURGERY was the second most cited journal with 10 520 citations in total. These journals have a strong reputation in the field of LT for liver cancer. According to the information from the Web of Science, categories of these journals were involved in Transplantation, Surgery, Gastroenterology, and Hepatology and Immunology. With the citing journals on the left of the map and the cited journals on the right, the dual-map overlay of journals in Figure 3 demonstrated the topic distribution of the journals. The dual-map overlay presents that almost all the articles about LT for liver cancer were published in one discipline ('medicine medical clinical'). The knowledge base of publications in this field are mainly the two disciplines on the right side of the map ('health nursing medicine' and 'molecular biology genetics').

Analysis of co-cited references

Co-cited references means that they were cited by more than one of the articles integrated into this study. To explore the background and knowledge base of LT for liver cancer, we analyzed the co-citations of references via CiteSpace. Figure 4A depicted the distribution network of co-cited references from 1963 to 2023, with references which were cited over 45 times labeled on the map. In addition, according to the color bar, the lighter the color of the node, the later it was cited.

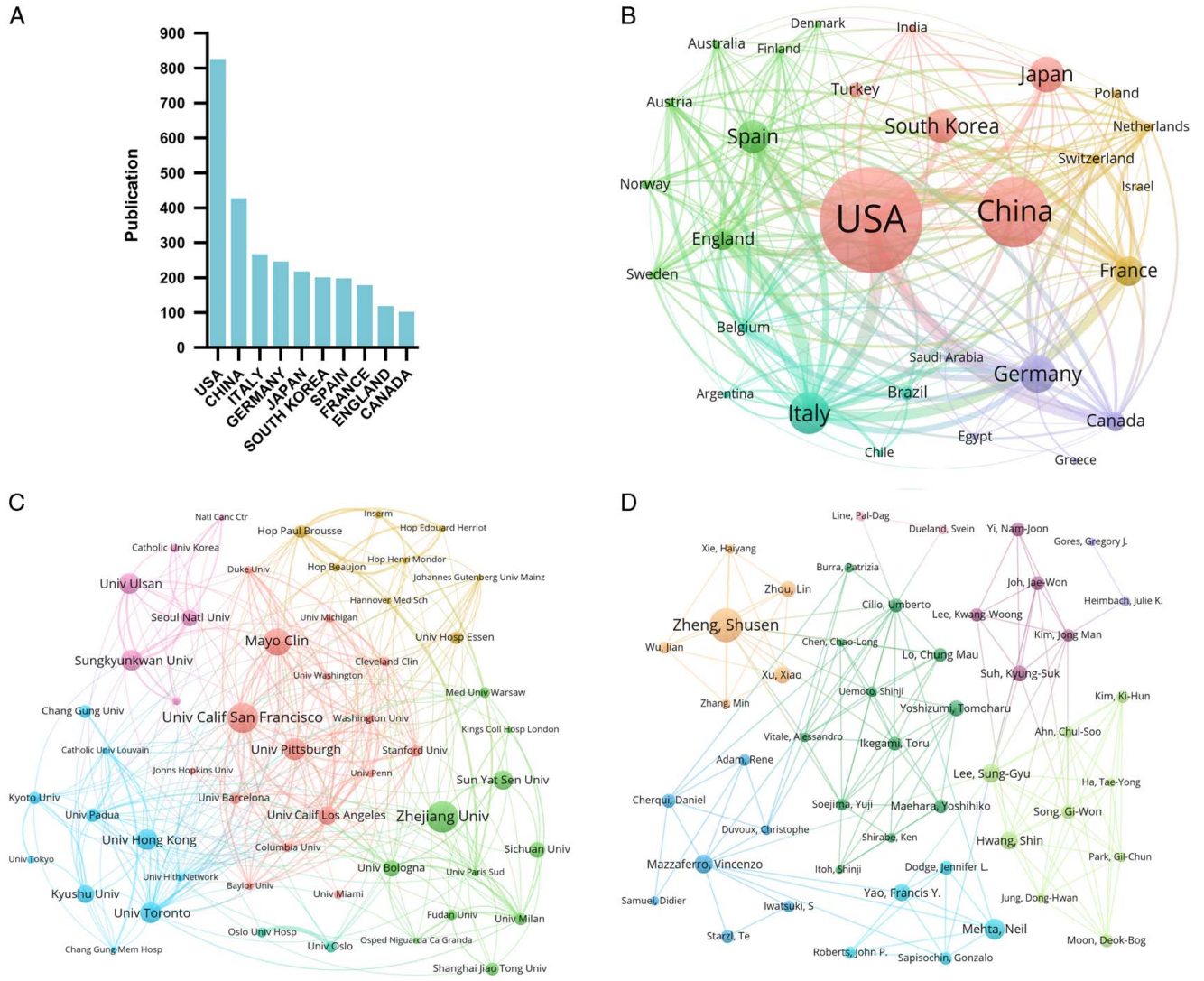

Figure 2. (A) The top 10 productive countries/regions. The network maps showing countries/regions (B), authors (C) and institutions (D) involved in the research on liver transplantation for liver cancer.

Table 4 listed the top 10 co-cited references. Among them, the paper entitled 'Predicting survival after LT in patients with HCC beyond the Milan criteria: a retrospective, exploratory analysis' has received the most number of co-citations ($n = 142$)[24]. The paper entitled 'Recommendations for LT for HCC: an international consensus conference report' ranked the second ($n = 109$)[25]. Both of the two articles were published on LANCET

Table 1

The top 10 productive institutions.

Institution	Publications	Citations
Assistance Publique Hopitaux Paris APHP	130	8145
Udice French Research Universities	114	6838
Mayo Clinic	85	4497
Zhejiang university	84	2552
University of California San Francisco	83	6519
Pennsylvania Commonwealth System of Higher Education Pcshe	68	4822
University of Padua	63	3759
Hopital Universitaire Paul Brousse Aphp	62	5539
University of Pittsburgh	62	4733
Institut National De La Sante Et De La Recherche Medicale Inserm	59	2264

Table 2

The top 10 productive authors.

Name	Country	Publications	Total citations	Per citations
Zheng, Shusen	China	69	2505	36.30
Cillo, Umberto	Italy	51	3390	66.47
Lee, Sung-Gyu	Korea	49	1556	31.76
Mazzaferro, Vincenzo	Italy	49	9790	199.8
Hwang, Shin	Korea	47	1295	27.55
Lo, Chung Mau	China	45	1956	43.47
Mehta, Neil	USA	44	1539	34.98
Yao, Francis Y	USA	43	5562	129.35
Joh, Jae-Won	Korea	41	1028	25.07
Xu, Xiao	China	40	831	20.78

Table 3

The top 10 journals of publications on liver transplantation for liver cancer (sorted by total citations).

Journal	Category	Impact factor (2022)	Total publications (%)	Total citations
Liver Transplantation	Gastroenterology & Hepatology; Surgery; Transplantation	4.6	214 (7.16)	13 814
Annals of Surgery	Surgery	9.0	64 (2.14)	10 520
Hepatology	Gastroenterology & Hepatology	13.5	53 (1.77)	8236
Transplantation	Immunology; Surgery; Transplantation	6.2	123 (4.11)	5458
Transplantation Proceedings	Immunology; Surgery; Transplantation	0.9	415 (13.88)	5017
American Journal of Transplantation	Surgery; Transplantation	8.8	58 (1.94)	3911
Journal of Hepatology	Gastroenterology & Hepatology	25.7	53 (1.77)	3676
Transplant International	Surgery; Transplantation	3.1	69 (2.31)	1436
Clinical Transplantation	Surgery; Transplantation	2.1	58 (1.94)	1118
Experimental and Clinical Transplantation	Transplantation	0.9	62 (2.07)	285

ONCOL. The top 10 co-cited references were all published after 2000, with about one-third of them published in the last decade.

According to the log-likelihood ratio algorithm of CiteSpace, a total of 28 clusters were identified. The 10 largest clusters among them were showed in Figure 4B. In the timeline view, different colored nodes on the same line indicate different years of references in a cluster, with the nodes closer to the right representing more recent references. The cluster labels are at the far end of the line. Modularity Q (0.9448) was greater than 0.3 and Mean Silhouette (0.9605) values was greater than 0.7, indicating that the clusters are convincing and structurally significant. The 10 largest clusters were labeled as 'hepatocellular carcinoma recurrence' (cluster #0), 'hepatocellular carcinoma' (cluster #1), 'unresectable liver tumor' (cluster #2), 'large hepatocellular cancer' (cluster #3), 'neoadjuvant chemotherapy' (cluster #4), 'metastatic neuroendocrine tumor' (cluster #5), 'c virus infection' (cluster #6), 'adult liver transplant candidate' (cluster #7), 'elevated level' (cluster #8) and 'alcoholic liver-disease viral-hepatitis' (cluster #10), respectively. Cluster #0 is the largest as well as the most recent cluster, containing 358 references.

The citation burst of references means that these references receive a significantly higher number of citations than usual over a period of time. And this type of analysis can help to explore how research hotspots changed over time. The top 50 with the strongest citation burst was showed in Figure 5, with the red bar indicating high citation frequency and the blue bars indicating fewer citations.

The reference with the strongest burst strength (strength = 58.63, burst period = 2010–2014) is 'Predicting survival after LT in patients with HCC beyond the Milan criteria: a retrospective, exploratory analysis' published by Mazzaferro *et al*.[24], same with the most co-cited reference. Table 5 showed the references which keep in a state of burst. We checked the status of all the mentioned papers and excluded inaccessible ones owing to the potential ethic concerns[26,27].

Analysis of keywords

Keywords represent the core contents of articles. Keywords co-occurrence analysis can be used to identify active areas of the research field. In a total of 4703 keywords from 2991 papers, the top 100 most frequent ones were extracted and clustered, with each keyword occurring at least 35 times (Fig. 6A). The average publishing year of these keywords were between 2006 and 2017. The different colors of the nodes represent the five different clusters found, containing 39, 25, 17, 10, and 9 keywords, respectively. Cluster 1 (pink) is mainly related to treatment strategies of liver cancer. Keywords in this cluster include 'liver transplantation', 'liver resection', 'immunosuppression', 'sirolimus', 'tacrolimus' and 'chemotherapy'. Cluster 2 (blue) contains keywords related to tumor recurrence and transplantation criteria, such as 'recurrence', 'milan criteria', 'alpha -fetoprotein', 'tumor size', 'living donor liver transplantation' and 'microvascular invasion'. Cluster 3 (green), Cluster 4 (yellow) and Cluster 5 (purple) focused on survival, outcome and hepatocellular carcinoma, respectively. In the density view (Fig. 6B),

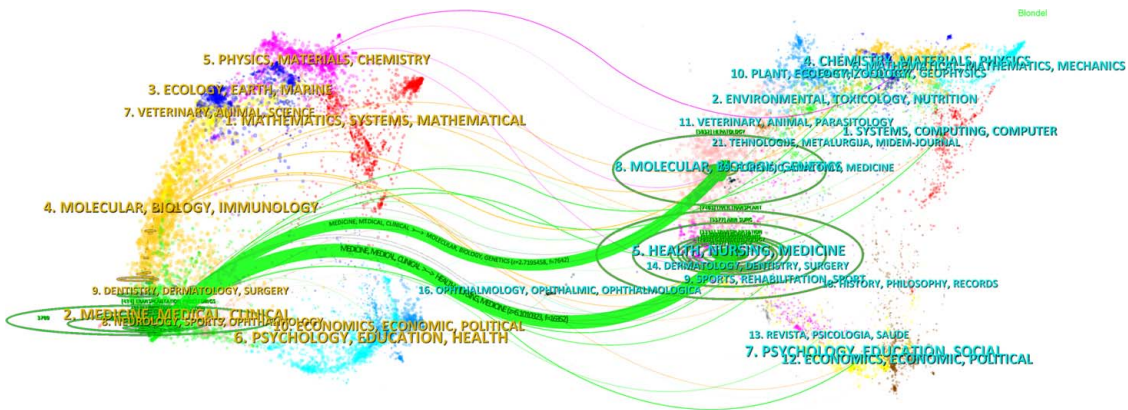

Figure 3. The dual-map overlay of journals.

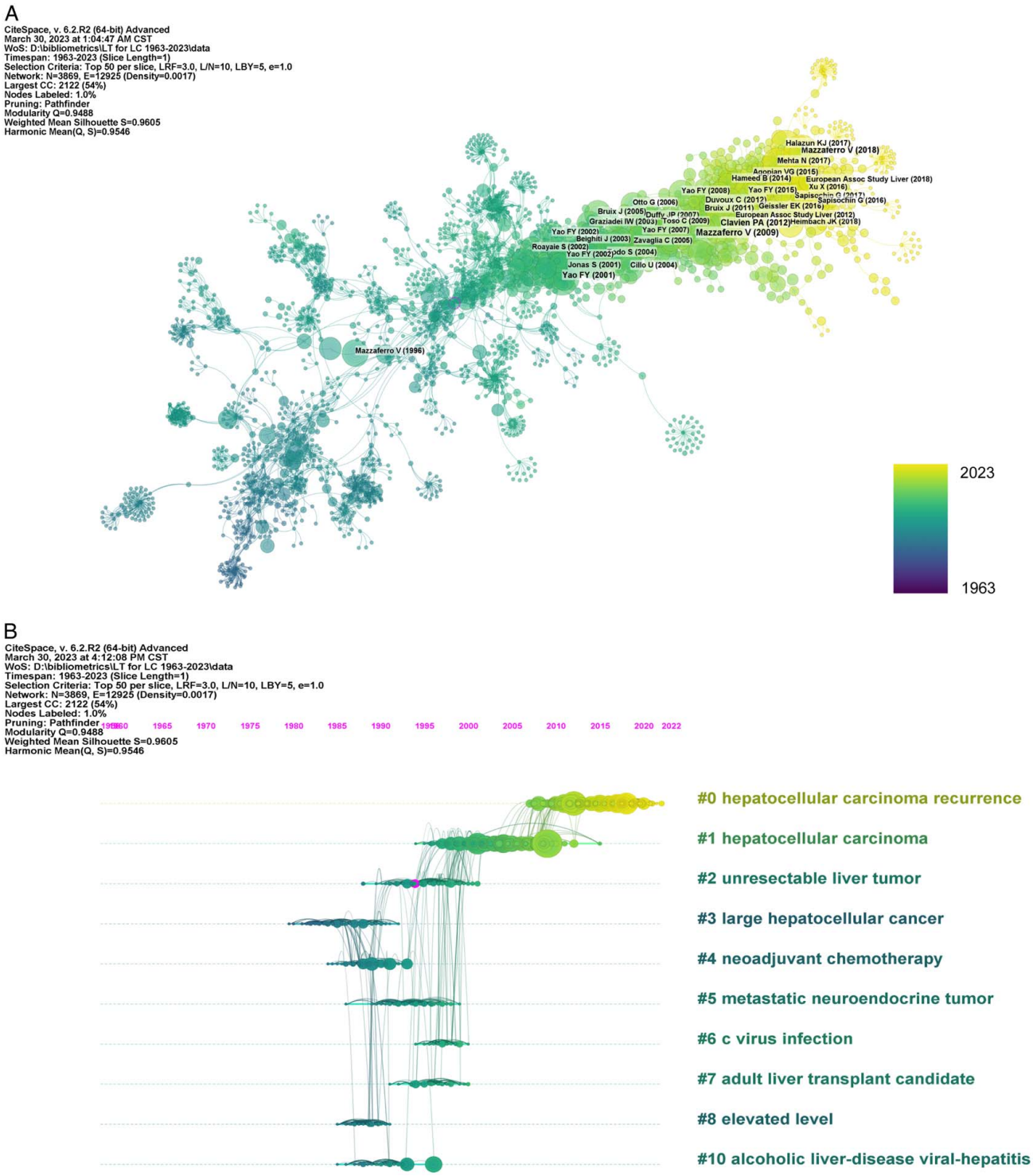

Figure 4. The map of co-citation references (A) and the largest 10 clusters (B).

'liver transplantation', 'hepatocellular carcinoma', 'recurrence', 'survival', 'resection', 'cancer' showed a high density in the map, indicating the significance of these topics and the potential interests of research in the field of LT for liver cancer.

We used the time view and the keyword burst to explore the evolution of research trend, predict emerging topics and reveal potential research hotspots. In Figure 6C, keywords were marked in different colors according to their average publishing year. Early-appearing keywords are displayed in white, while recent keywords are displayed in dark purple. The most recent keywords included 'hcc', 'alpha-fetoprotein', 'sorafenib'. 'mortality', 'candidates', 'locoregional therapy' and 'outcomes'. Figure 6D showed the keyword burst in the field of LT for liver cancer over the last two decades. The keywords that were still in a state of burst are 'model',

Table 4

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First author	Year	Journal	Title	Co-citations
Mazzaferro, *et al.*[24]	2009	Lancet Oncol	Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis	142
Clavien, *et al.*[25]	2012	Lancet Oncol	Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report	109
Mazzaferro, *et al.*[48]	2018	Gastroenterology	Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma	96
Yao, *et al.*[32]	2001	Hepatology	Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival	90
Duvoux, *et al.*[84]	2012	Gastroenterology	Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria	73
Halazun, *et al.*[44]	2017	Ann Surg	Recurrence After Liver Transplantation for Hepatocellular Carcinoma: A New MORAL to the Story	70
Bruix, *et al.*[85]	2011	Hepatology	Management of hepatocellular carcinoma: an update	69
Mehta, *et al.*[45]	2017	JAMA Oncol	Validation of a Risk Estimation of Tumor Recurrence After Transplant (RETREAT) Score for Hepatocellular Carcinoma Recurrence After Liver Transplant	68
Todo, *et al.*[86]	2004	Ann Surg	Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan	67
Jonas, *et al.*[87]	2001	Hepatology	Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis	67

'validation', 'score', 'liver transplant', 'death', 'sorafenib', 'safety', suggesting the potential research hotpots in the future.

Discussion

In this study, we conducted a systematic literature search of the WOSCC database for articles in LT for liver cancer published between 1963 and 2023. Further, bibliometric visualization has been executed based on the 2991 papers published in 531 journals from 70 countries/regions.

The field of LT for liver cancer has been developing for decades since 1963 when Dr. Starzl attempted to treat unresectable liver cancer with liver transplant for the first time[1]. However, LT has not been widely applied for a long time due to numerous obstacles such as organ rejection and immature surgical techniques[28]. This is consistent with our analysis of the articles published in this field. With the development of immunosuppressive strategies and the maturation of surgical protocols, LT has gained global popularity rapidly since 2000 and has demonstrated an important role in the management of liver cancer, which is evidenced by the significant increase in the number of publications and citations (Fig. 1B). The growing collaboration at home and abroad also indicates that research in this field is continuing to deepen. Based on the current understanding of tumor biology, giant progresses have been made in improving the clinical outcomes of LT for liver cancer, with indications extended. The in-depth analysis of the citation burst of references and keywords in the last two decades revealed that the focus of this field in the past decades and in the future perhaps remains on the precise selection of recipients, as well as the prevention and treatment for tumor recurrence after LT.

The role of LT in the treatment of liver cancer was still controversial in the 1990s, when numerous studies focused on the comparison between LT and liver resection. Studies have found that patients with HCC who received LT demonstrated better survival rates in cases of liver damage or cirrhosis, making LT an effective treatment for small, unresectable HCC in patients with cirrhosis[29–31]. These encouraging findings gradually promoted the application of LT in the treatment of liver cancer. Further, the Milan criteria (single tumor ≤ 5 cm in size or ≤ 3 tumors each ≤ 3 cm in size, and no macrovascular invasion) was proposed by Mazzaferro *et al.*[31] in 1996, and became the benchmark to ensure clinic benefits of HCC recipients. However, according to the rigid Milan criteria, a great number of HCC patients, might benefit from LT, would be excluded. Several studies have tried to expand the criteria, while maintaining prognosis. Among the top 10 most cited articles (Table 6), Yao *et al.*[32] put forward University of California San Francisco (UCSF) criteria, with the total tumor diameter extended to 8 cm and single tumor largest diameter extended to 6.5 cm. Mazzaferro led a retrospective study of 1556 HCC recipients from 36 centers and proposed up-to-seven criteria, with similar 5-year survival rates compared to the Milan criteria[24]. With the deeper understanding of tumor biology, more studies have tried integrating HCC biomarkers, including alpha-fetoprotein (AFP), des-γ-carboxyprothrombin (DCP), and γ-glutamyl transpeptidase (GGT), into the expended criteria for increasing the number of eligible HCC patients[33,34]. A multicenter retrospective study, leaded by the group from Zhejiang University, utilized AFP for precise prognostic stratification. 6012 HCC recipients, fulfilling Hangzhou criteria, were divided in to Hangzhou type A and type B according to AFP <100 ng/ml and tumor burden, thus realizing delightful clinical outcomes in Hangzhou type A LT recipients (with 5-year recurrence-free survival 69.5%)[35]. Many other studies also indicated AFP as a potent prognostic risk factor and enlarge the population of LT candidates, including but not limited to 5-5-500, total tumor volume (TTV)/AFP, and the LiTES-HCC score[36–38]. Moreover, Kyoto criteria, incorporating DCP ≤ 400 mAU/ml, successfully expanded criteria in living donor LT for HCC with the 5-year OS and recurrence rate 82% and 7%, respectively[39]. And Malatya criteria, as well as Expanded Malatya criteria, incorporated GGT and achieved comparable prognosis of HCC recipients enrolled with that within Milan criteria[40,41]. Overall, criteria for selecting LT candidates with HCC should adequately incorporate multidimensional parameters, including tumor burden and cancer molecular characteristics. Perhaps gene mutation and imaging features would also be integrated in the selection criteria for better candidates choosing.

As presented in Figure 4B, cluster #0, labeled 'hepatocellular carcinoma recurrence', is the largest and most recent cluster in the reference co-citation analysis, indicating a sustained interest in

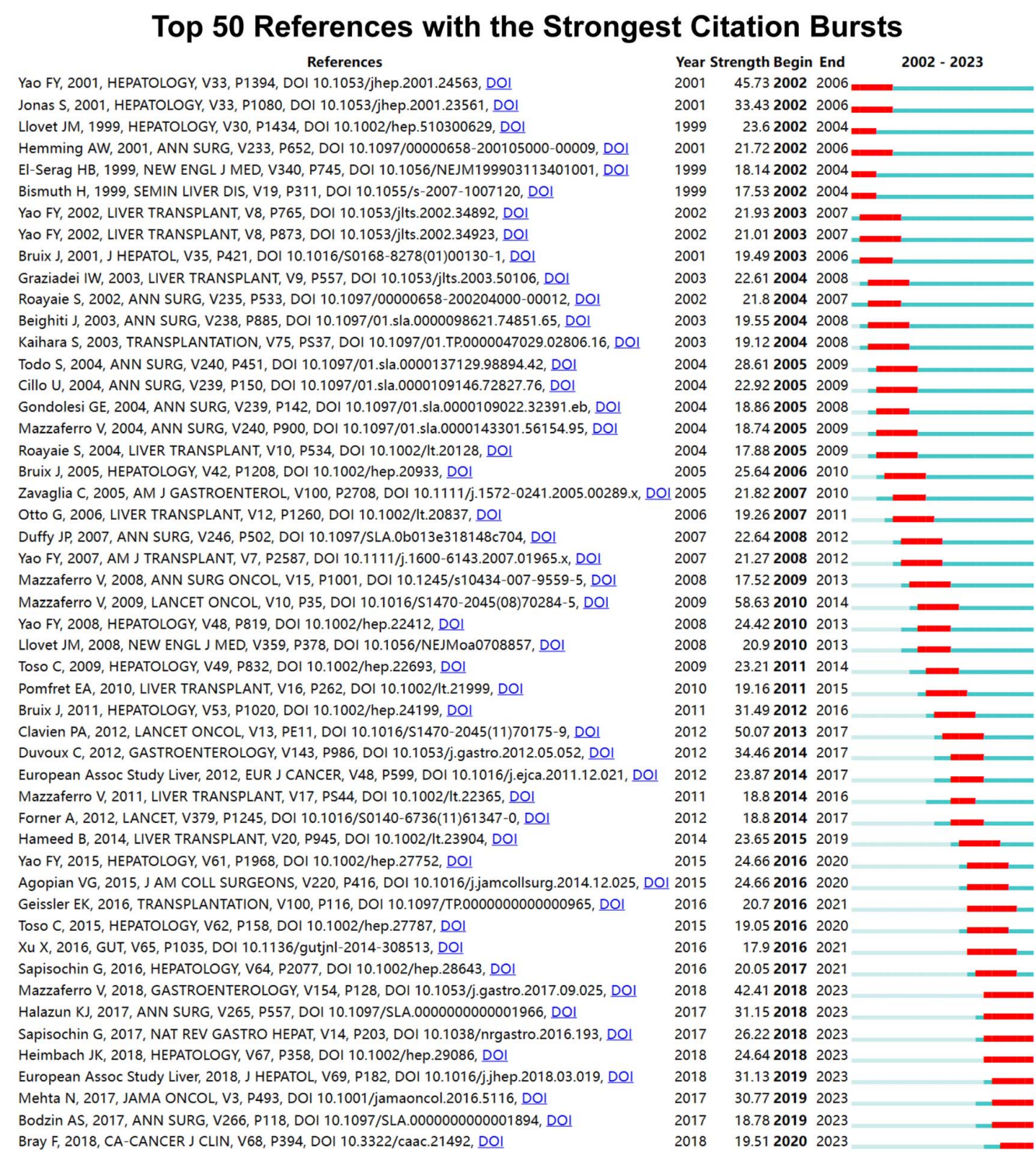

Figure 5. Visual analysis of references bursts.

this topic among clinicians and academicians. The tumor recurrence rate after LT was reported to range from 10 to 25% and significantly affect the outcomes of patients[42,43]. Three papers in burst status also were with respect to this hotspot (Table 5)[44–46]. These three prediction models incorporated tumor burden, tumor biology, recipient health status, and other parameters (like donor serum sodium), which all showed excellent performance in the recurrence prediction. Moreover, many other models, such as the R3-AFP score[47] and Metroticket 2.0 model[48], have been built mainly based on tumor burdens and tumor biology. Though the parameters involved were simplified, these models also helped with identifying recipients in high risks for recurrence and making clinical decisions. Furthermore, dynamic evaluation of biomarkers has been found to predict tumor recurrence. Halazun

Table 5

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Burst period	First author	Year	Journal	Title
2018–2023	Mazzaferro, *et al.*[48]	2018	Gastroenterology	Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma
2018–2023	Halazun, *et al.*[44]	2017	Ann Surg	Recurrence After Liver Transplantation for Hepatocellular Carcinoma: A New MORAL to the Story
2018–2023	Sapisochin, Bruix[11]	2017	Nat Rev Gastro Hepat	Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches
2018–2023	Heimbach, *et al.*[88]	2018	Hepatology	AASLD guidelines for the treatment of hepatocellular carcinoma
2019–2023	European Association for the Study of the Liver[89]	2018	J Hepatol	EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma
2019–2023	Mehta, *et al.*[45]	2017	JAMA Oncol	Validation of a Risk Estimation of Tumor Recurrence After Transplant (RETREAT) Score for Hepatocellular Carcinoma Recurrence After Liver Transplant
2019–2023	Bodzin, Adam S[46]	2017	Ann Surg	Predicting Mortality in Patients Developing Recurrent Hepatocellular Carcinoma After Liver Transplantation: Impact of Treatment Modality and Recurrence Characteristics
2020–2023	Bray, *et al.*[90]	2018	CA-Cancer J Clin	Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

et al. put forward the New York/California (NYCA) score, which incorporated dynamic AFP response for the first time and was superior in predicting recurrence-free and OS compared with existing HCC-related selection tools[49]. The construction of the aforementioned models reflected a gradually deepening understanding of HCC biology, also referred to as transplant oncology. Among the top 10 most cited articles, Yang *et al*. found that high expression of the long non-coding RNA HOTAIR was an independent risk factor for post-transplant recurrence in HCC patients, which suggest it a promising biomarker for predicting tumor recurrence and treatment target against HCC[50]. Moreover, liquid biopsy could detect peripheral nucleic acids, proteins and cells, which undoubtedly help with post-transplant monitoring in a noninvasive manner. A research group from Shanghai detected preoperative and postoperative circulating tumor cells (CTCs) of 193 patients and found the predictive value of CTCs for tumor recurrence in patients with HCC following LT[51]. Also, multiomics technologies such as mass cytometry, proteomics, transcriptomics, radiomics, and metabolomics, can be powerful tools to explore the mechanisms of tumor development and identify key molecule or cell cluster in cancer recurrence[52–55].

The citation burst of references also indicated downstaging/bridging therapy as a matter of concern. Downstaging/bridging therapy refers to reducing the tumor burden to meet the transplant criterion or preventing tumor progression during the waiting donor liver so that better post-transplant outcome would be achieve[56,57]. Graziadei and colleges executed a prospective study and found that trans-arterial chemo-embolization (TACE) followed by LT was found to be associated with excellent outcomes in selected patients, with 1-year, 2-year, and 5-year survival rates of 98, 98, and 93%. Meanwhile, TACE is also efficacious in tumor progression prevention during the waiting period[58]. Otto *et al*.[59] assessed the role of TACE in selecting patients with tumors suitable for LT, which showed that a sustained response to TACE could be a better criterion for LT than the size or number of tumors initially assessed. Compared with TACE, some clinical trials have indicated that trans-arterial radio-embolization (TARE) seems to performed better in tumor control with similar safety profile[60,61]. Besides advances in locoregional therapy, systemic therapy, especially immunotherapy (including immune-checkpoint inhibitors, and immune cell therapy), also have driven increasing attention in the downstaging/bridging therapy pre LT[62]. However, immunotherapy which has clinical potential as a neoadjuvant treatment prior to LT, are required large multicenter clinical trials to provide further data on safety, especially the usage duration and elution time[63,64].

Also, from the keywords burst we found that sirolimus-based immunosuppression has also gained attention. The use of mammalian targets of rapamycin (mTOR) inhibitors may decrease post-LT tumor recurrence and metastasis in recipients with HCC. A prospective randomized trial found that treatment with sirolimus over 3 months improved the prognosis of HCC patients undergoing LT, particularly for those with AFP $\geq$ 10 ng/ml[65]. It has also been found that the combination of mTOR inhibitors with targeted drugs, such as sorafenib, has a synergistic antitumor effect, which could be a promising regimen to treat recurrence of HCC after LT[66,67]. However, a certain number of HCC recipients with specific gene mutant or overexpression would not benefit from mTOR inhibitors[68,69]. For more precise

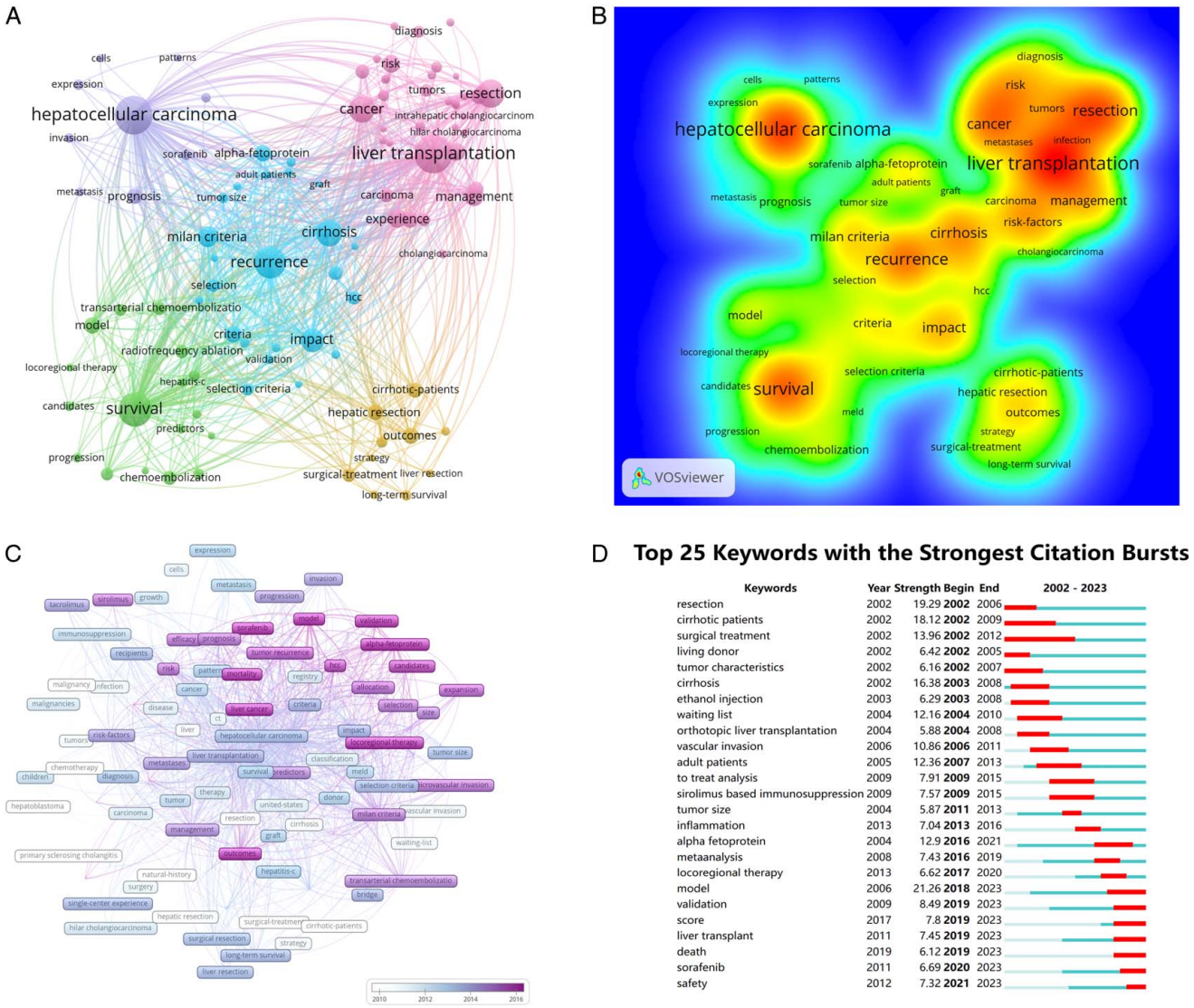

Figure 6. (A) The network map of top 100 keywords with 5 clusters. (B) The density view and (C) the time view of the map of keywords. (D) The keywords with the strong citation bursts in articles related to liver transplantation for liver cancer.

administration of immunosuppression, there has been a gradual shift from protocol-based immunosuppression regimens to personalized ones which take recipient characteristics, the etiology of the liver-disease and the extent of alloimmune activation into account in order to approach optimal transplant immunosuppression[70].

Besides HCC, there have been increasing attention in LT for other types of gastrointestinal tumors, such as cholangiocarcinoma (CCA), CRLM and neuroendocrine tumor (NET) owing to attractive potential clinical benefit[71,72]. Because of the poor outcomes led by early recurrence, CCA used to be an absolute contraindication for LT. With improvement in patient selection criteria and neoadjuvant treatment protocols, several studies have demonstrated favorable results with LT for a selected group of ICC patients with small lesions (usually referred to diameter less than 2 cm) as well as patients with inoperable perihilar CCA[73,74]. For CRLM, especially unresectable metastases, current evidence has suggested a survival benefit conferred by LT compared to palliative chemotherapy. However, the acceptable criteria need further refinement and the ethical implications of organ availability and allocation still remain to be rigorously justified due to the scarcity of donor grafts[75,76]. More clinical studies, with prospective design and high-level evidence, are encouraging to be performed to put forward consensus or guideline on LT eligibility criteria for gastrointestinal tumors.

Besides the aforementioned, the expansion of the donor pool , ex vivo organ preservation (including machine perfusion), xenotransplantation, transplant tolerance, and de novo malignancies after LT are also common concerns in the field of LT[77–82].

Conclusion and Perspective

There is no doubt that LT has become an important method of treatment against liver cancer. This global overview of publications in this field using bibliometric methods and visualization

Table 6

Please refer to the newly uploaded version.

Title	First author	Journal	Year	Total citations	Citations per year
Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis	Mazzaferro, *et al.*[31]	New England Journal of Medicine	1996	5158	184.21
Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival	Yao, *et al.*[32]	Hepatology	2001	1621	70.48
Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis	Mazzaferro, *et al.*[24]	Lancet Oncology	2009	1375	91.67
Liver Resection Versus Transplantation for Hepatocellular Carcinoma in Cirrhotic Patients	Bismuth, *et al.*[30]	Annals of Surgery	1993	772	24.9
Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis	Jonas, *et al.*[91]	Hepatology	2001	748	32.52
Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function - Implications for a strategy of salvage transplantation	Poon, *et al.*[92]	Annals of Surgery	2002	703	31.95
Overexpression of Long Non-coding RNA HOTAIR Predicts Tumor Recurrence in Hepatocellular Carcinoma Patients Following Liver Transplantation	Yang, *et al.*[50]	Annals of Surgical Oncology	2011	593	45.62
Liver Transplantation for Hepatocellular Carcinoma: A Model Including α-Fetoprotein Improves the Performance of Milan Criteria	Duvoux, *et al.*[84]	Gastroenterology	2012	574	47.83
Hepatic Resection Versus Transplantation for Hepatocellular Carcinoma	Iwatsuki, *et al.*[29]	Annals of Surgery	1991	537	16.27
Nonalcoholic Steatohepatitis Is the Most Rapidly Growing Indication for Liver Transplantation in Patients With Hepatocellular Carcinoma in the US	Wong, *et al.*[93]	Hepatology	2014	501	50.1

tools to reveal the changes and developments in this field over the past decades. Meanwhile, LT for liver cancer is an important part of transplantation oncology, which is a novel and comprehensive discipline formed by the intersection and integration of various disciplines such as surgery, oncology, and immunology. The four E-pillars of transplant oncology were proposed in 2021, foreseeing the main directions of transplant oncology in the diagnosis and management of hepatobiliary malignancies[83]. In the future, research related to this field should focus on focal problems such as recipient selection for LT and tumor recurrence after LT, with multidisciplinary thinking and making full use of multiomics techniques, promoting active cooperation among research groups from different disciplines. All in all, we hope findings both in the bench and bedside would help with precise management of LT recipients and achieving a better prognosis.

Ethical approval

Not required.

Consent

Not required.

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Author contribution

X.X., X.H., and S.X.: designed the research; X.H. and S.X.: collected and organized data; X.H., S.X., and L.T.: analyzed the data; X.H., S.X., L.T., S.L., and X.W.: drafted the manuscript; X.X., S.L., and X.W.: contributed to the critical revision of the manuscript. All authors contributed to the manuscript and approved the submitted version.

Conflicts of interest disclosure

Authors declare no conflict of interest.

Research registration unique identifying number (UIN)

Not required.

Guarantor

Xiao Xu.

Provenance and peer review

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Data availability statement

The data in this study is not of a confidential nature and is accessible in the public domain.

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