A bibliometric analysis of gastric cancer liver metastases: advances in mechanisms of occurrence and treatment options

Chenyuan Wang, BS[a], Yuzhe Zhang, MS[b], Ye Zhang, MD[b,*], Baifeng Li, MD[c,*]

Background: Gastric cancer (GC) is the fifth most commonly diagnosed cancer worldwide, and its poor prognosis is predominantly attributed to distant metastasis. The liver is the primary site of GC metastasis. However, there is no universally approved treatment regimen for liver metastasis in GC. The aim of this article is to review the current research status and trends of liver metastasis of GC worldwide.

Methods: The authors utilized the Web of Science Core Collection database to identify articles on liver metastasis from GC published between 2000 and 2022. The authors used bibliometric methods to analyze authors, institutions, countries, journals, and references through CiteSpace and VOSviewer. A total of 1003 articles were included in this study.

Results: Japan published the most articles in the field, followed by China. Nagoya University is the leading institution in the field of liver metastases in GC. Yasuhiro Kodera from Japan has made significant achievements in this area. The authors identified GC to be the most influential journal in this field. Using cluster analysis, the keywords were divided into four major clusters:(1) the molecular mechanism of GC liver metastasis, (2) prognosis, (3) liver resection, and (4) chemotherapy.

Conclusion: Our study systematically summarizes the results of GC liver metastasis research from 2000 to 2022 and describes and predicts research hotspots and trends on a global scale. Research on the molecular mechanisms of GC liver metastasis will become a hot topic in the future, and the expansion of the surgical treatment scope and the advancement of translational therapy will benefit more patients.

Keywords: bibliometric, gastric cancer, liver metastasis, molecular, resection

Introduction

Gastric cancer (GC) is the fifth most commonly diagnosed cancer and the third leading cause of cancer-related death worldwide and was responsible for more than 1 000 000 new cases and 782 000 deaths in 2018[1]. The clinical prognosis of patients with GC has significantly improved over the years with advancements in diagnostic techniques and therapeutic methods[2]. Radical surgical resection, neoadjuvant therapy, and chemotherapy are the primary treatment options for GC. These approaches are

HIGHLIGHTS

- This study was the first bibliometric analysis in the gastric cancer (GC) of liver metastasis surgery field.
- Using leading analytical methods in the field of bibliometrics, we explore the current status and hotspots of research in the field of liver metastasis from GC and predict future research hotspots.
- Molecular mechanisms, prognosis, hepatic resection, and chemotherapy are the main research directions in the field of GC liver metastasis.

intended to prolong patient survival and improve their quality of life, but some clinical studies have revealed that these approaches do not sufficiently improve prognosis[1,3–5]. However, once metastases develop, whether the metastatic site is the liver or not, the prognosis is poor[6–13]. The most common sites of metastasis for GC include the liver, peritoneum, and bones[14–16]. Based on the anatomical relationship between the liver and stomach, GC cells can achieve liver metastasis through the unique blood supply system and hemodynamic structure of the liver[17]. According to the Surveillance, Epidemiology, and End Results (SEER) database, approximately 34% of patients have distant metastasis, and 4–14% of patients present with liver metastases as the initial signs or symptoms of GC[18,19].

Gastric cancer with liver metastases (GCLM) is considered a stage IV b disease, according to clinical guidelines issued by the National Comprehensive Cancer Network (NCCN). The prognosis of GCLM is poor, with a 5-year survival rate of less than

[a]Department of Urology Surgery, [b]The First Laboratory of Cancer Institute and [c]Department of Hepatobiliary Surgery, The First Hospital of China Medical University, Shenyang, People's Republic of China

Chenyuan Wang and Yuzhe Zhang contributed equally to this work and are co-first authors.

Ye Zhang and Baifeng Li are co-response authors.

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*Corresponding author. Address: NO.155 Nanjing Street, Heping District. Tel.: +139 400 419 75. E-mail: zhangyecmu@163.com (Y. Zhang), and Tel.: +150 024 201 96. E-mail: libaifeng818@163.com (B. Li).

10%[20]. The rate of liver metastasis in patients with advanced GC is exceptionally high, and studies have shown that ~37% of patients who undergo resection for GC and were followed up for distant recurrence develop liver metastases[21]. GCLM is a significant prognostic factor for GC, highlighting the importance of studying liver metastasis in the clinical treatment of advanced GC. Therefore, gaining a comprehensive understanding of the mechanisms, treatment strategies, and prognostic factors of GCLM is crucial for the management of advanced GC[22].

In this study, we used bibliometric methods to analyze articles related to GCLM from 2000 to 2023, outlined current research trends in the treatment of GCLM, and analyzed and predicted future research hotspots.

Material and methods

Database and search strategy

We sourced all publications for our study from the Web of Science Core Collection (WOSCC), which includes more than 12 000 highest-impact, top-quality scientific journals. Figure 1 shows the specific data retrieval techniques and inclusion processes used in this study. The search tactics are shown in Figure 1. The articles were published between 1 January 2000 and 31 December 2022. English-language articles and reviews were included in the manuscript.

Data analysis

The title, authors, year of publication, country/region, institution, keywords, citations, abstracts, and references were obtained from the WOSCC database. The downloaded files were in a plain text format. Journal Citation Reports (JCR) 2021 was used to calculate the impact factor. Two researchers used the VOSviewer 1.6.18 program to extract all data that qualified for inclusion in this study, and then imported it into CiteSpace 5.7.R5 and Microsoft Excel 2019. The traditional bibliometric analysis

program, VOSviewer, used to perform visualized analysis in bibliometric research[23]. CiteSpace can be used to examine the co-occurrence and centrality of collaborative networks between countries, authors, and institutions[24]. VOSviewer can be accessed at https://www.vosviewer.com/getting-started, where detailed instructions regarding its use are available. Citespace can be accessed and downloaded at https://citespace.podia.com/, where text tutorials and video tutorials on its use are available. provides text tutorials and video tutorials for using this software. The Tableau Desktop software was used to present the differences in publication volume between the countries.

Results

Analysis of the number of publications and citations

From 2000 to 2020, there were 1003 papers on GCLM, according to comprehensive manual screening. The numbers of publications and citations are shown in Figure 2. We observed that the number of papers published continued to increase from the year 2000 onward and peaked at 2015 (70 papers) and then stabilized between 2016 and 2022.

Analysis of contributions of prolific authors and co-cited authors

Table 1 shows that only one author from China made up the majority of the top 10 most prolific authors in this discipline. Most of the top 10 co-cited authors were from Japan, with the remainder coming from China and the United States.

A collaborative network of authors with more than five publications is shown in Figure 3. There were 11 clusters on the network visualization map (Fig. 3(A)). Kodera Yasuhiro was the top author with the highest number of links (total links = 153) in the study. According to the overlay map, two new study teams were established based on Chinese scholar Chen Wen-Liang and Japanese scholar Kanda Mitsuro (Fig. 3(B)). In Figure 3(C), we
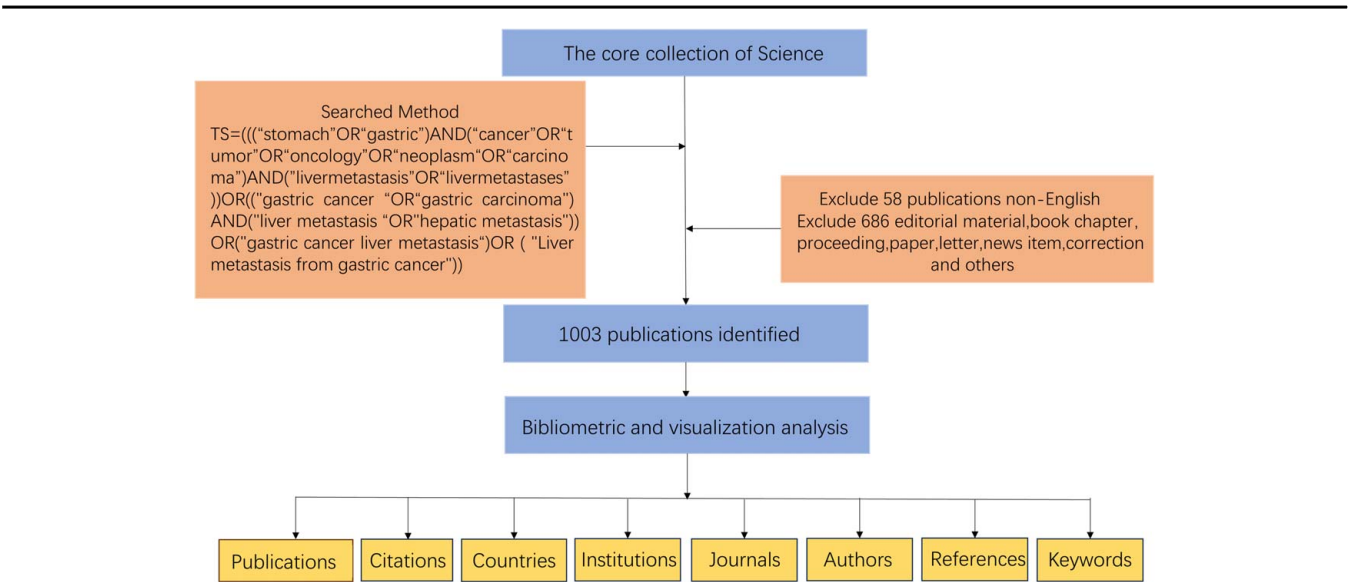

Figure 1. Detailed flowchart steps of the search strategy in screening publications.

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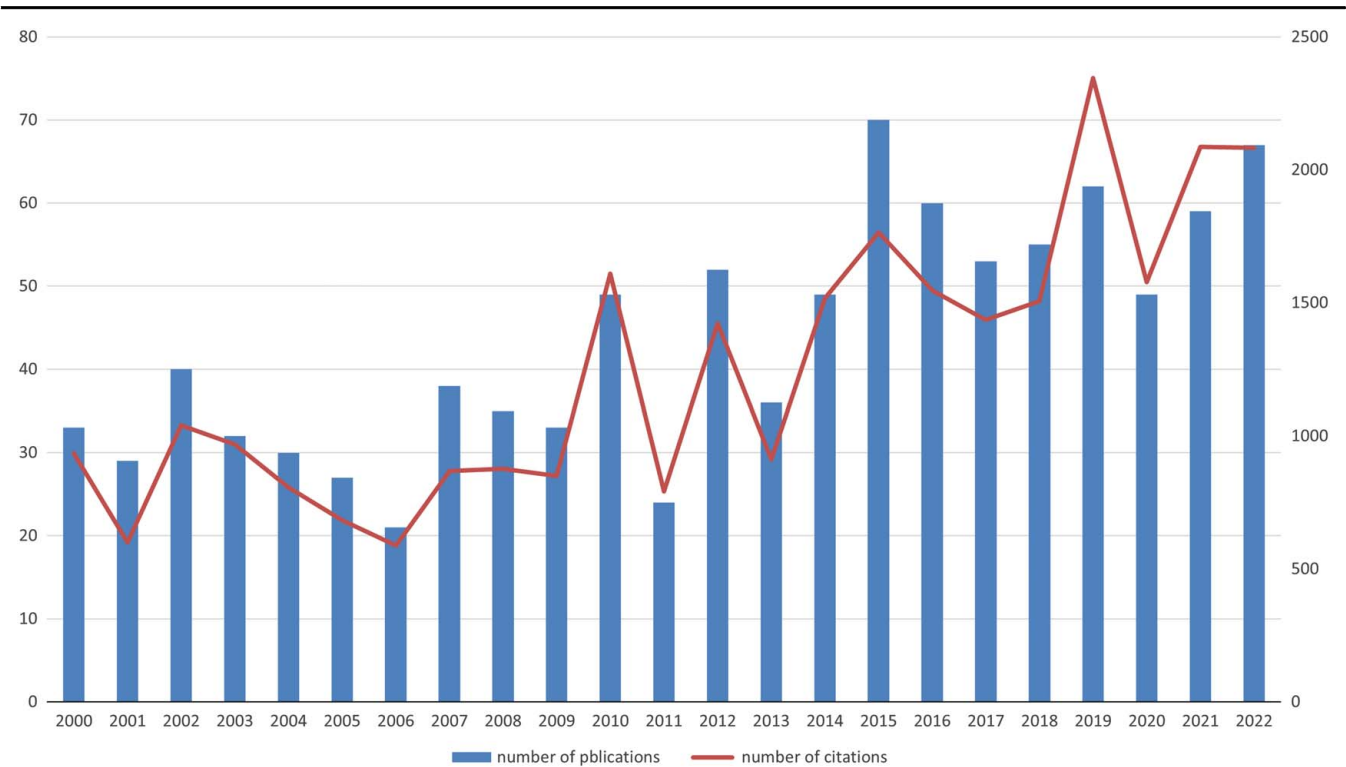
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Figure 2. The annual number of publications and citations on gastric cancer with liver metastases from 2000 to 2022.

show the relationship between the top 20 authors, their countries and the affiliated institutions.

Analysis of the contributions of journals

To show the distribution of citing and cited journals, we employed a dual-map overlay atlas. In Figure 4, the citing journal was represented by the geographic area on the left, and the cited journal was represented by the map on the right. The hues of the lines served as markers for different disciplines. The cited journals mostly dealt with molecular, biology, genetics, nursing, surgery, and chemistry, whereas the cited journals mainly dealt with mathematics, medicine, clinical, biology, and immunology.

A total of 373 journals published articles or reviews in this field. We list the 10 most productive journals with their average citation and total publication number in this field in Figure 5. Among the top 10 journals, most were JCR Q1 and Q2.

Analysis of the contributions by institutions

Figure 6(A) displays the top 10 productive institutions, with five each in China and Japan. The minimum number of institutional publications was set to five, and the VOSviewer was used to identify 84 institutions contributing to the examination of institutional co-authorship. The institutional co-authorship network, composed of 84 institutions and organized into 16 clusters, is shown in Figure 6(B). In recent years, Chinese institutions have shown a growing influence in the GCLM field. This is evident from the overlay map (Fig. 6(C)) of the historical trend for the number of articles.

Analysis of the contributions of countries

Figure 7 shows the participation of 47 countries and regions in the geographical distribution of global publications in the

Table 1

Top 10 prolific authors and co-cited authors.

Rank	Author	Country	Documents	Citation	Average article citation	H-index	Co-cited author	Country	Total citation
1	Yasuhiro Kodera	Japan	21	495	23.571	65	Sakamoto,Y et al.[25]	Japan	186
2	Chie Tanaka	Japan	15	377	25.133	32	Okano,K	Japan	127
3	Mitsuro Kanda	Japan	14	298	21.285	42	Bang,YJ et al.[26]	China	114
4	Masamichi Hayashi	Japan	13	285	21.923	29	Koizumi, W et al.[27]	Japan	113
5	Yamada Suguru	Japan	13	289	22.23	42	Ajani, JA	USA	102
6	DaisukeKo bayashi	Japan	12	350	29.166	31	Maehara, Y	Japan	98
7	Nakayama Goro	Japan	11	201	18.272	36	Ambiru,S et al.[28]	Japan	93
8	Shen, Lin	China	11	736	66.909	57	Adam,R	France	92
9	Michitaka Fujiwara	Japan	9	306	34	43	Chang,YC	China	89
10	Haruyoshi Tanaka	Japan	9	195	21.666	17	Miettinen,M	USA	87

Figure 3. Co-authorship analysis of the excellent authors in the field of GCLM. (A) A network visualization map. (B) A overlay visualization map. (C) Countries and institutions of these distinguished authors.

GCLM field. Figure 8(A) compares the publishing trends of the top five nations with those of the rest of the world over time. Figure 8(B) illustrates the examination of co-authorship among these 21 countries using VOSviewer. As shown in Figure 8(C), China has recently engaged in considerable research cooperation.

Figure 4. The dual-map overlay of journals related to gastric cancer with liver metastases.

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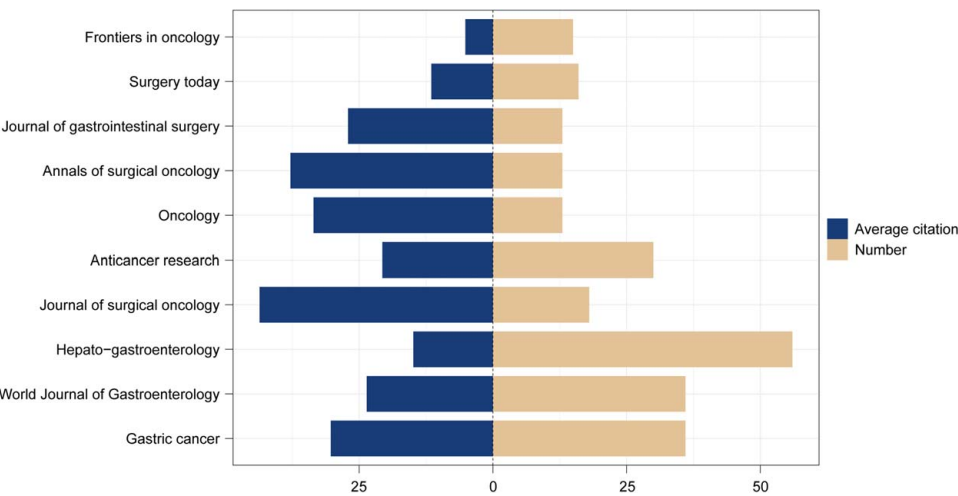
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Figure 5. The average citation and total publication number of the top 10 journals.

Analysis of a highly cited study

The top 10 articles with the highest citation frequencies are listed in Table 2. The article titled 'Hepatic resection for metastatic tumors from GC' published in the Annals of Surgery in 2004 was cited the most. Out of 21 763 references 51, articles were cited more than 30 times are shown in Figure 9.
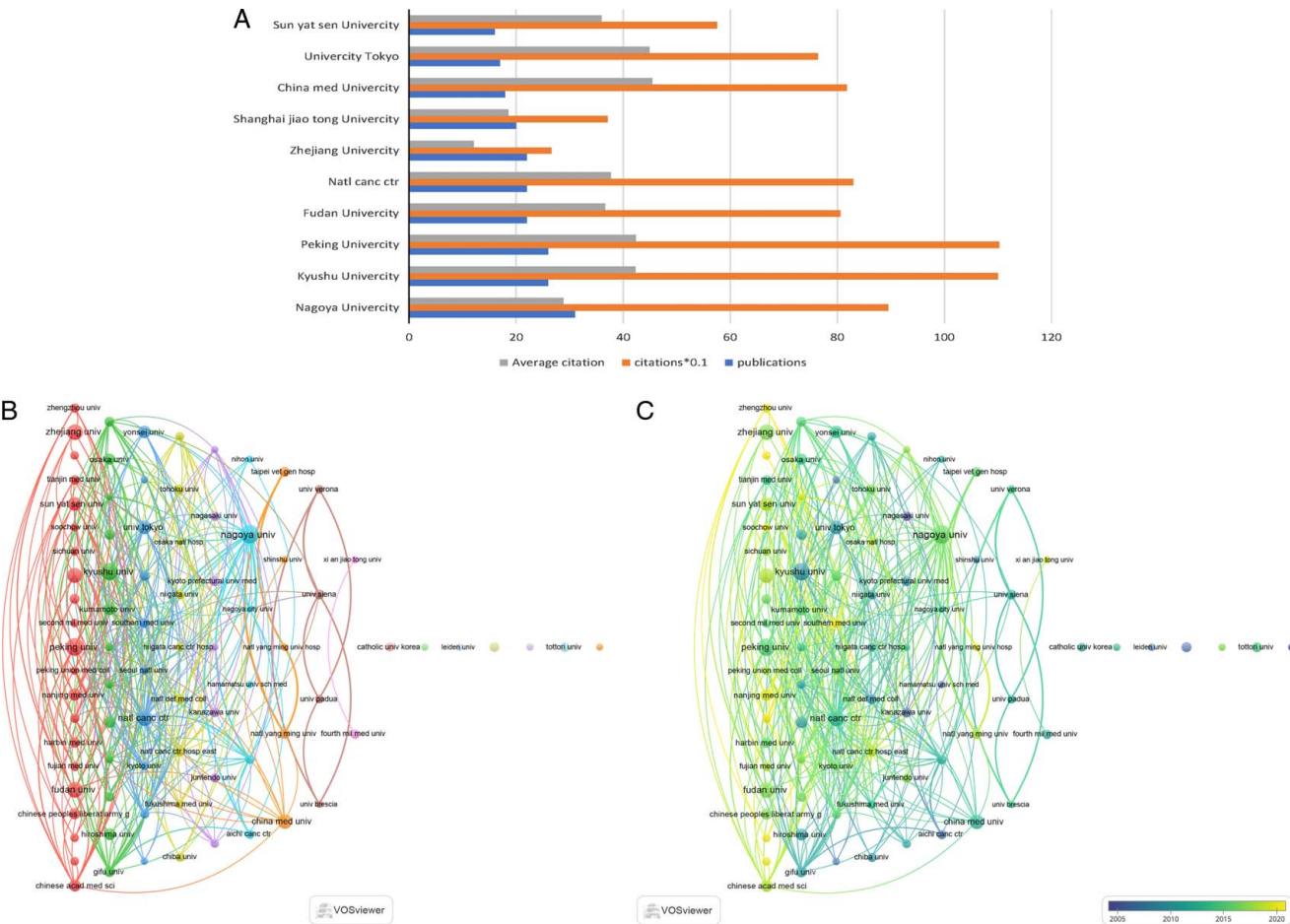

Figure 6. (A) The total number of publications, the average number of citations, visualization map. (B) A network visualization map. (C) A overlay visualization map.
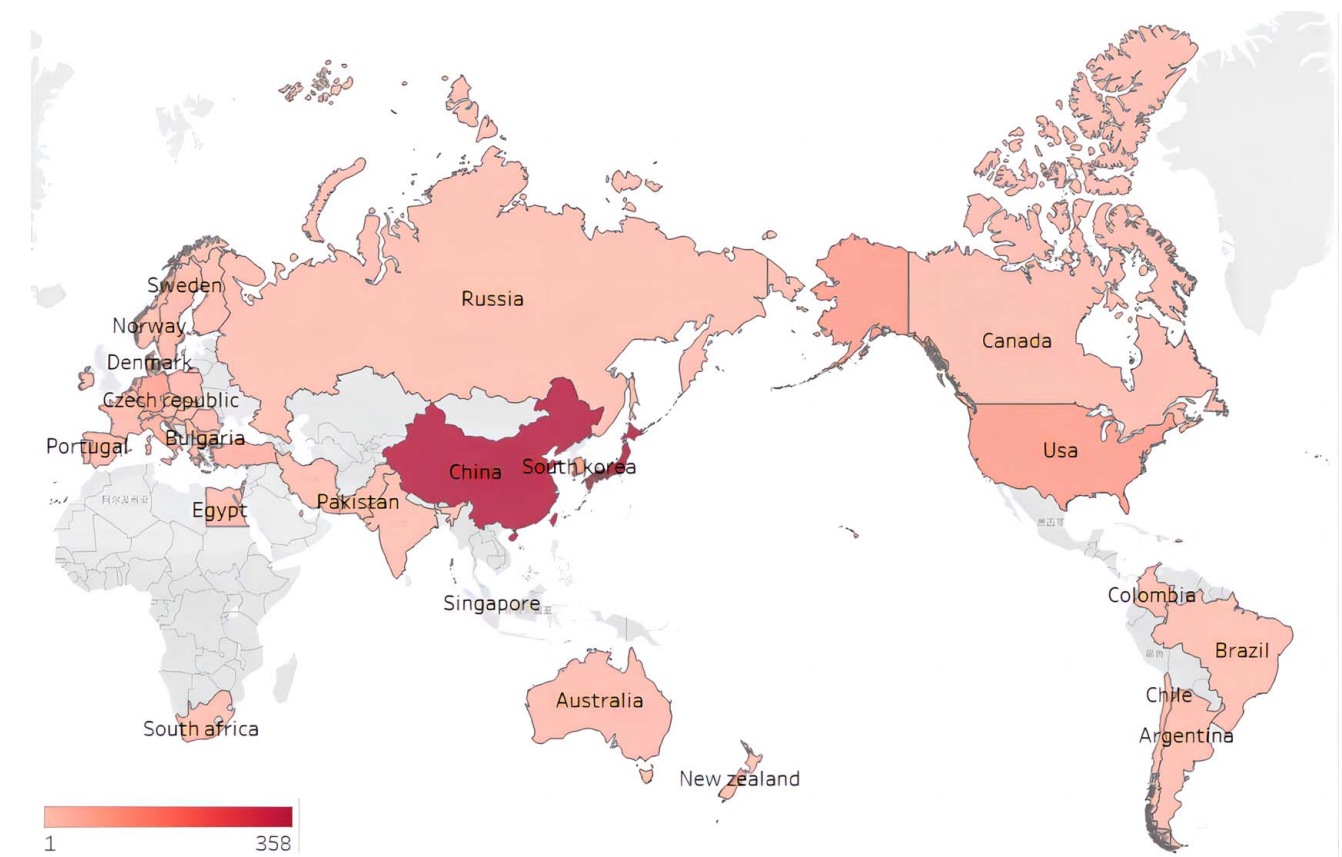
Figure 7. Geographic distribution of global publications on gastric cancer with liver metastases. World map showing the distribution of global publications on gastric cancer with liver metastases.

Analysis of keywords

Figure 10(A) shows keywords with a frequency of higher than 10. In total, 166 high-frequency keywords were selected from 1003 studies, and divided into five clusters. We selected four major clusters from the five clusters for analysis. Cluster 1 (red cluster): molecular mechanism of GCLM, including gene expression, protein, and angiogenesis; cluster 2 (blue cluster): prognosis, including mutation, prognosis factors, diagnosis; cluster 3 (yellow cluster): liver resection, include survival, resection, recurrence, liver metastasis; cluster 4 (green cluster): chemotherapy, include clinical trial, nivolumab. The timeline picture can show the period and time trend of different research keywords. According to Figure 10(B), invasion, advanced GC, hepatectomy, and alpha-fetoprotein, are the longest-lasting hotspots, which lasted from 2000 to the present. Burst word analysis can reveal hot research in a research field during a specific period. We show the top 25 keywords with the strongest citation bursts in Figure 10(C). In Figure 10(D), the top five keywords with the highest occurrences across the four major clusters.

Discussion

Global research status and trends

According to the analysis of national publication data, China, Japan, and South Korea, three Asian nations, have contributed a significant number of publications totaling 757, accounting for 75.5% of the total literature. Furthermore, the data on the total connection strength between authors reveal that the top three authors are from Japan, indicating the formation of a tightly-knit and influential group of authors within Japan. From the perspective of journal publications and citations, GC stands out as a significant journal in the field of GCLM research, with papers of great importance and reference value.

In our analysis of the top 10 institutions, we observed that half were from China and the other half were from Japan. The top three institutions are Nagoya University, Kyushu University, and Peking University.

Research keyword analysis

Through cluster analysis of 166 keywords that appeared more than 10 times, keywords were divided into four main clusters, cluster 1 (red cluster): molecular mechanism of GCLM, cluster 2 (blue cluster): prognosis, cluster 3 (yellow cluster): liver resection, cluster 4 (green cluster): chemotherapy. These keywords in the co-occurrence analysis can show the main research directions and hot topics of researchers in this field. By analyzing the timeline graph of keywords and top 20 outbreak words, we can observed that keywords related to molecular mechanism, prognosis, and surgical treatment appeared with high-frequency from 2000 to 2022, indicating that the study of molecular mechanism and the exploration of surgical treatment have always been the hotspot of
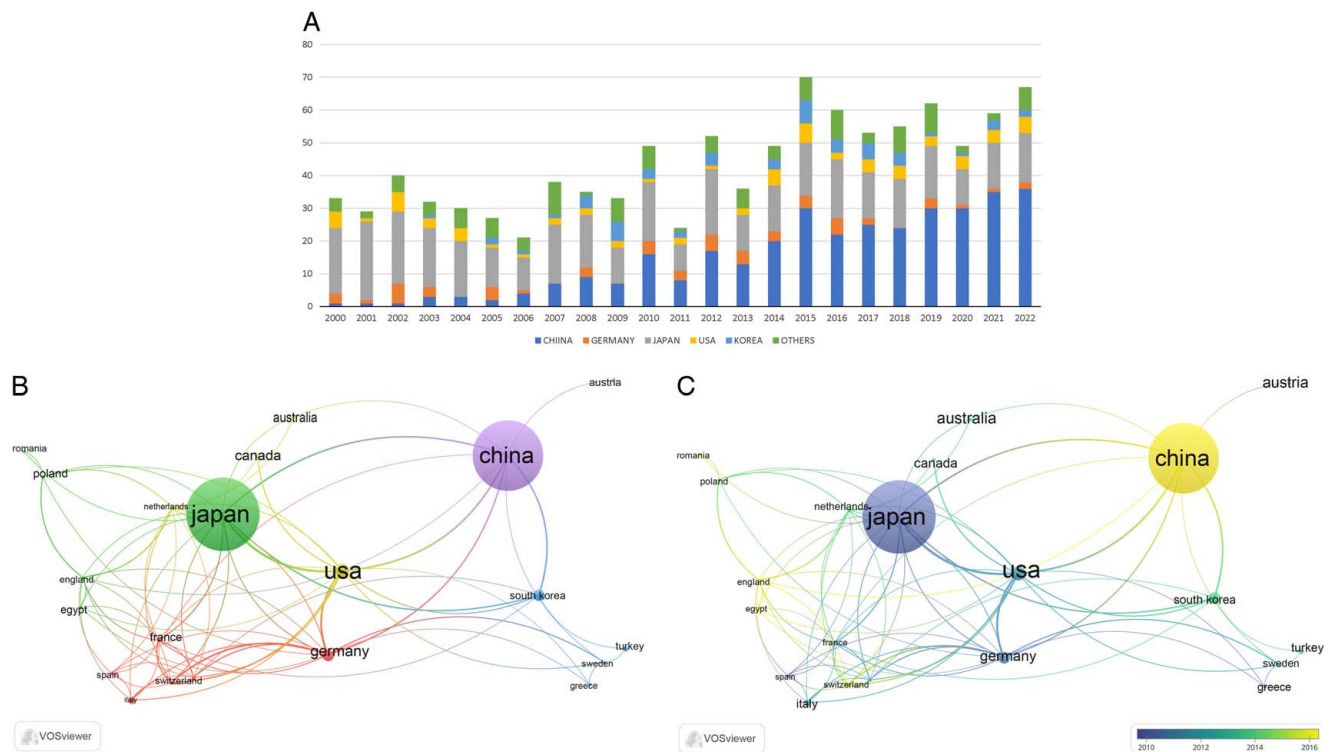
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Figure 8. (A) Bar graph of the top five productive countries/regions. (B) Network visualization map of the top 21 countries' collaboration. (C) Overlay visualization map.

the research. Additionally, in recent years, chemotherapy-related studies have also gradually occupied an important position, and these studies are often tightly coupled with prognostic analyses, which is also in accordance with the results of our clustering analysis. We analyze the above four clusters to explore the research hotspots and directions in the field of GCLM.

Red cluster: molecular mechanism of GC liver metastasis

With advances in molecular biology, researchers investigating cancer metastasis have discovered that the development of liver metastasis requires numerous complex cellular processes, including local GC cell infiltration and erosion, which are transferred to the survival of the liver microenvironment and colonization[34]. Multiple signaling cascades have also been shown to play a role in colonization and metastasis[35]. According to Misuro Kanda, SYT7 is a driver of liver-metastatic GC. In SYT7 deletion mice, the incidence of liver metastasis was greater.

Tumor microenvironment (TME) means that the occurrence, growth, and metastasis of tumors are closely related to the internal and external environment of tumor cells. It has been proved that signal molecules secreted by tumor cells in TME through autocrine or paracrine pathways can promote cancer metastasis[36]. Exosomes are components of the TME, and previous studies have confirmed that they are signaling molecules that mediate the metastasis of many other cancers[37,38]. Qiu et al.[39] demonstrated that exosomes could promote liver metastasis of GC by enhancing M2-like macrophage-mediated angiogenesis. According to a study by Deng et al.[40], the TMEM200A may act as an adhesion molecule in the TME during the spread of GC.

Many researchers have found that methylation modification, overexpression of extracellular vesicles, and gene regulation can promote liver metastasis in GC[41–43]. According to previous studies, PCSK9 can control the production of HSP70 and promote cell death to prevent metastasis of GC[44]. Mei et al.[45] in vitro cell experiments confirmed that the Snail-miR590-VEGFR-NRP1 axis inhibits GC cell invasion and metastasis. HOXC10 of NF - kB pathways through regulation can contribute to the erosion and transfer of GC cells[46]. Moreover, Ikari et al.[47] found that TP53 gene mutations were correlated with liver metastasis through gene sequencing of GC cells, but the specific mechanism has not been clarified.

Blue cluster: prognosis

The reason for the low 5-year survival rate could be that some patients missed the best chance for therapy because they were already in an advanced stage with extensive liver metastases at the time of evaluation. Researchers have been looking for the early identification and intervention of liver metastases. The study by Baba et al. demonstrated that PRAME, a target gene, was screened by genetic analysis and screening of tissues from patients with liver metastases from GC and correlation with clinical information. Thus, PRAME can be used as a new biomarker to predict GCLM (AUC 0.713)[48].

In addition to studies on early prediction, many studies have focused on how to effectively evaluate the prognosis and prolong the survival time of patients with GCLM. The specific prognosis of GC with liver metastasis makes it difficult to achieve a good prediction effect by simple clinical staging. A study of the American Joint Committee on Cancer (AJCC) staging scheme has

Table 2

The top 10 co-citation references related to Gastric cancer with liver metastases.

Rank	Year	First author	Title	Source	Citations
1	2001[28]	Ambiru S	Benefits and limits of hepatic resection for gastric metastases	The American Journal of Surgery	86
2	2010[26]	Bang YJ	Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial	Lancet	87
3	2008[29]	Cheon Sh	Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases	Annals of Oncology	83
4	2007[30]	Koga R	Liver resection for metastatic gastric cancer: Experience with 42 patients including eight long-term survivors	Japanese Journal of Clinical Oncology	67
5	2008[27]	Koizumi W	S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial	Lancet Oncology	76
6	1997[28]	Miyazaki M	Hepatic resection of liver metastases from gastric carcinoma	American Journal of Gastroenterology	71
7	1994[31]	Ochiai T	Hepatic resection for metastatic tumors from gastric cancer: analysis of prognostic factors	British Journal of Surgery	78
8	2002[32]	Okano K	Hepatic resection for metastatic tumors from gastric cancer	Annals of Surgery	122
9	2003[33]	Sakamoto	Surgical resection of liver metastases of gastric cancer: an analysis of a 17-year experience with 22 patients	Surgery	89
10	2007[25]	Sakamoto Y	Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer.	Journal of Surgical Oncology	93

The data in this study is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature. All the data could be contact with the corresponding author: libaifeng818@126.com with scientific purpose.

also proved that a personalized prognostic evaluation scheme is very necessary[49]. Dong et al.[50] constructed a nomogram for prognostic analysis by collecting and analyzing the clinical information of patients with GCLM in the SEER database. Because the patient data in the SEER database only includes the patient's age, sex, tumor stage, survival time, etc., it does not take into account the biochemical indicators produced by liver metabolism, such as alkaline phosphatase, bilirubin, etc., which have been proved to be related to the prognosis[51–53]. Therefore, Feng et al.[54] incorporated liver biochemical indicators into the construction of the prediction model in their study, and also obtained good results. In addition, Hori et al.[55] also established a prognostic grading model for patients with GCLM based on the influence of computed tomography. In addition to the above-mentioned studies on the establishment of prognostic models, many scholars have evaluated the prognosis of patients with GCLM with different gene mutations. In HER2(+) patients, surgical resection after trastuzumab treatment can effectively improve prognosis[56].

Yellow cluster: liver resection

Hepatectomy for liver metastases from colorectal cancer has been recognized as an effective treatment modality, with a 5-year survival rate of 30–50%. However, its effect on GC liver metastasis is not yet exact[32]. Most current guidelines suggest systemic chemotherapy or radiofrequency ablation as the initial course of treatment for individuals with GCLM. However, a clinical experiment conducted by Japanese researchers revealed that the 5-year survival rate of patients who received systemic chemotherapy as their only course of treatment was only 1.7%[57]. Such outcomes are undesirable, and systemic chemotherapy alone is unlikely to improve patient prognosis or extend patient survival. According to a Japanese publication on liver metastases from GC, careful selection of patients for hepatectomy may be advantageous for some patients[58]. A study by Sakamoto et al. reported that patients with unilobar metastases or metastases with a diameter of less than 4 cm should undergo liver resection to obtain a better prognosis. Moreover, synchronous liver metastasis is no longer a contraindication to surgical resection[25]. This approach has also been recognized by other research groups[59]. For patients with metachronous liver metastasis from GC, the study of Satoshi Ambiru and Keiichi Okano suggested that adequate hepatectomy was necessary and could improve the prognosis[28,32]. In recent years, multicenter and long-term cohort studies using statistical methods for the surgical treatment of GCLM have been conducted, and an increasing number of studies have shown that surgical treatment is effective for the treatment of GCLM[10,60–62]. The study by S.-H et al.[63] also proved that different analyses have reported that surgery has a favorable impact on patients. A meta-analysis by Marte et al.[64], recommended that patients be treated with surgical resection and expressed a positive view on the future of conversion surgery, suggesting that guidelines may change in the future as the FLOT 5 trial advances.

With the progress in multidisciplinary treatment strategies in recent years, conversion surgery for GCLM has attracted increasing attention. Conversion surgery was defined as chemotherapy followed by R0 resection of oncologically or technically unresectable tumors. Yoshida et al.[65] also confirmed that patients with advanced GC, particularly those with liver
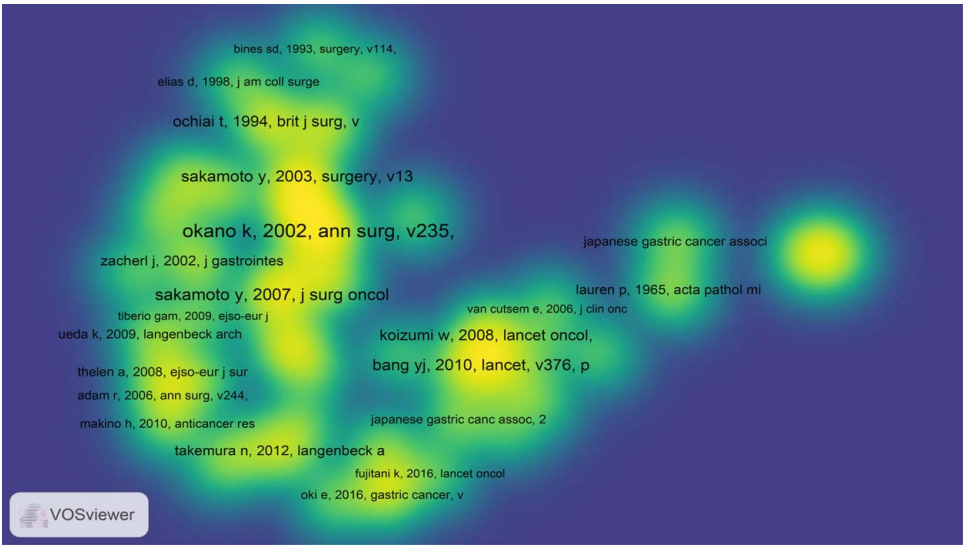
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Figure 9. Density visualization map of the top 51 co-cited references.

metastasis, could benefit from conversion surgery. Several case reports on conversion therapy have also demonstrated that the majority of patients go into remission after conversion surgery[66–68]. Research on conversion surgery will become a new hotspot in the future. These studies will guide clinicians to select patients who may benefit from surgical treatment more precisely.
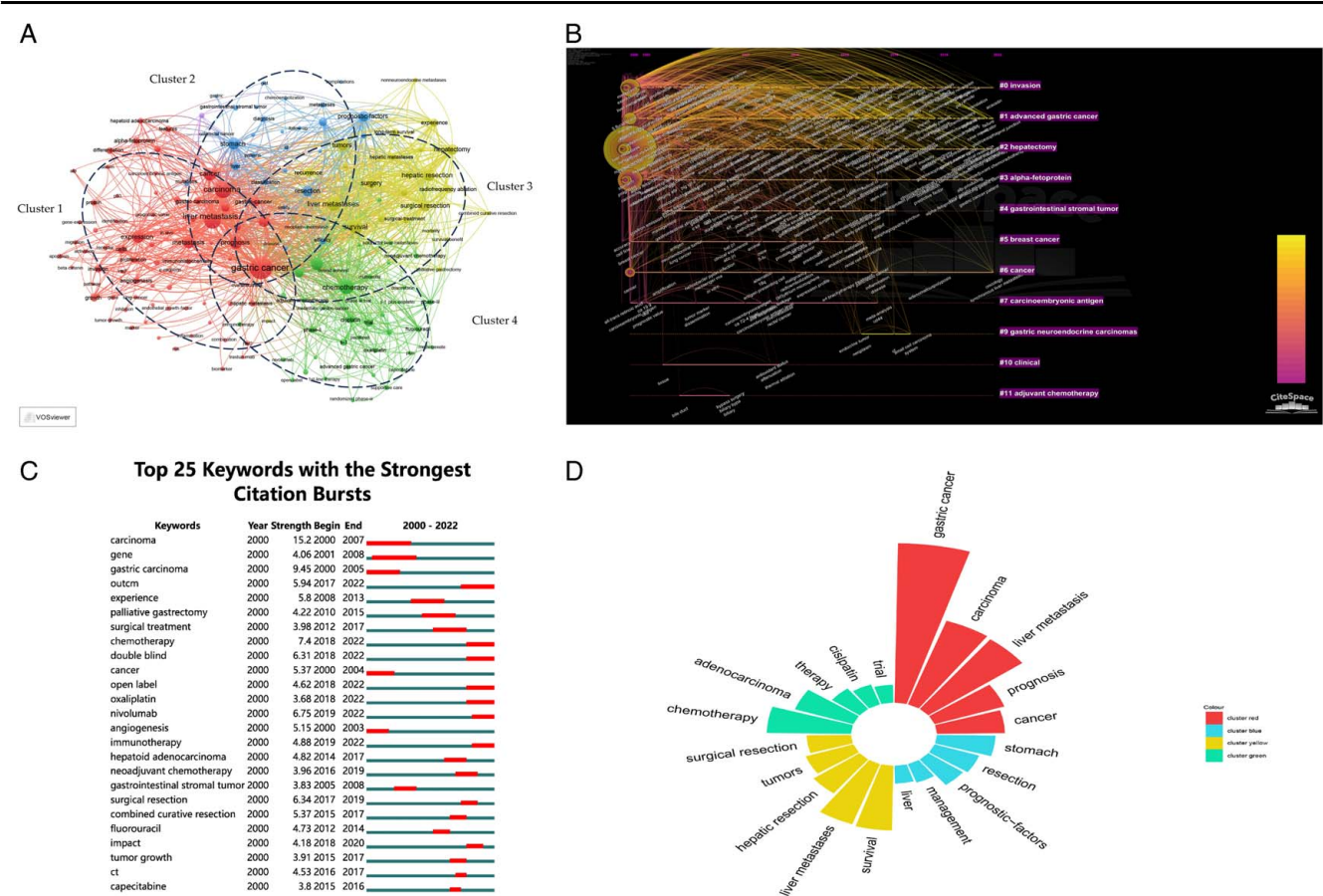

Figure 10. (A) A network visualization map. (B) A timeline and keyword clustering display for the GCLM. (C) The top 25 terms with the most significant gastric cancer with liver metastases citation bursts. (D) Keywords that are particularly important in the four groups.

Green cluster: chemotherapy

Some individuals with late-diagnosed GC already have significant distant metastases at the time of initial diagnosis, or the tumor is resistant to excision. Chemotherapy may be the only option for extending the life of these patients. The most popular chemotherapy regimens are dual or triple combinations of fluoropyrimidines, platinum derivatives, taxanes, or anthracyclines. Fluoropyrimidine with a platinum drug, along with docetaxel or anthracyclines, is currently the most common chemotherapy regimen for patients with GC with distant metastases[69,70]. SPIRITS clinical trial by Koizumi et al.[27] revealed that S-1 plus cisplatin was the most effective treatment for metastatic GC. With the development of immunotherapy and genetic testing, chemotherapy is different from the uniform treatment in the past and tends to be more individualized and precise. With the development of immunotherapy and genetic testing, chemotherapy differs from the uniform treatment in the past and tends to be more individualized and precise. Bang et al.[26] identified trastuzumab as a standard treatment for patients with HER2(+) metastatic GC in a multicenter phase III clinical trial. In addition to the studies on first-line treatment drugs mentioned above, many scholars have conducted research on second and third-line drugs[71–73].

As we have already exposed, many academics have realized that new approaches to treating GCLM have been made possible by the recent introduction of translational therapy and the use of hepatic resection. Preoperative FLOT in GC patients with minimal liver metastases has also been shown to be effective in a recent clinical trial in Germany[74]. The best course of treatment for individuals with only liver metastases is preoperative chemotherapy and hepatectomy, according to the results of a multicenter experiment conducted by European and Japanese researchers[75]. Docetaxel, cisplatin, and S-1 (DCS) combination chemotherapy was shown to be associated with a good prognosis in patients undergoing conversion surgery by Sato et al. research[67]. The studies mentioned above have shown that chemotherapy is a necessary and essential component for treating GCLM. Chemotherapy is essential for halting tumor growth and stabilizing systemic conditions. Second, chemotherapy offers an alternative course of treatment for more individuals who qualify for life-changing surgeries. There are still many unresolved problems regarding the selection of chemotherapy drugs for metastatic GC, which will be a focus of research in the future.

Limitations

Our bibliometric study has some limitations. First, only English literature was included in this study, important literature in other languages was not included in the analysis. Second, recently published high-quality articles cannot attract sufficient attention because of their short publication time and low citation frequency.

Conclusion

Based on a bibliometric study of liver metastasis in GC, we determined that the field of GCLM has received increasing attention from researchers. In terms of the output and quality of papers, Japan is the most influential country in this field in terms of paper output and quality. A comprehensive analysis of the number of publications and citations showed that GC was the most influential journal. According to the annual publication data, the number of publications in the field of GCLM has been increasing since 2000 and peaked in 2015 and stabilized thereafter. From this, we anticipate that research in the field of GCLM will continue to main a focal research in the future. And by analyzing the keywords, we evaluated four main research directions in the field of GCLM and the research trends they represent. The study of the GCLM mechanisms has become a popular area of research. Advances in prognostic analysis have also been recognized by an increasing number of scholars, and the mutual advancement and combined application of the two will lead to greater development of individualized patients' assessment. The expansion of surgical indications and standardization of clinical management techniques have prolonged the survival time of an increasing number of patients, and the application of translational therapy has provided critically ill patients the opportunity to benefit from surgery, and the improvement and updating of translational therapy protocols will be focus of research in the future.

Author contribution

C.W. and Y.Z.: research design; C.W. and Y.Z.: data collection; C.W., B.L., and Y.Z.: data analysis; C.W., B.L., Y.Z., and Y.Z.: manuscript preparation; C.W. and Y.Z.: manuscript editing. All authors confirm that they contributed to manuscript reviews and critical revision for important intellectual content, and read and approved the final draft for submission. All authors agree to be accountable for the content of this study. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: not required.
2. Unique identifying number or registration ID: not required.
3. Hyperlink to your specific registration (must be publicly accessible and checked): not required.

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Guarantor

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Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Provenance and peer review

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