



## Review article

# A bibliometric analysis of indocyanine green (ICG) in hepatobiliary surgery from 2008 to 2021

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## ABSTRACT

Hundreds of scientific documents have reported on the application of indocyanine green (ICG) in hepatobiliary surgery in the past 13 years, but few bibliometric studies have been conducted. This study aimed to identify the situations of authors, countries/regions, institutions, journals, and hot topics in this field. The overall status and prospects of the current research in this field can be elucidated by bibliometric analysis. Publications from 2008 to 2021 were retrieved from the Web of Science (WoS) Core Collection. The search terms included “liver,” “hepatic,” “gallbladder,” “bile duct,” “surgery,” “hepatectomy,” “ICG,” “indocyanine green,” and related synonyms. The full records of the search results were exported in text, and the cooperation network and hot topics were evaluated and visualized using CiteSpace software. The number of publications increased between 2008 and 2021. A total of 1527 publications were included in the results, and the frequency of citations was 30,742. The largest proportion of the publications emanated from Japan, and the majority of the papers were published by Kokudo. Tian Jie contributed the largest number of papers in China. Research was relatively concentrated among one country/region. The latest hotspots, “preservation” and “resistance”, frequently occurred. Cooperation between authors, countries, and institutions needs to be strengthened for high-quality research. Recent studies have focused on hepatectomy, bile duct resection, liver transplantation, and tumors in this field. Future research may focus on other aspects, such as liver preservation and resistance.

## 1. Introduction

With the rapid development of hepatobiliary surgery in recent years, an increasing number of treatment methods for benign and malignant liver diseases have been developed [1–6]. Nonetheless, surgery remains the primary treatment approach for hepatobiliary surgery [7]. A major challenge of hepatobiliary surgery is the need to maximize the preservation of the liver parenchyma [8]. Therefore, the intraoperative localization of liver segments and hepatic lesions is crucial for reducing postoperative morbidity,

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mortality, and complications [9]. Various intraoperative visualization methods have been proposed in recent decades to improve surgical accuracy and reduce postoperative complications [10]. Indocyanine green (ICG) is the most commonly used contrast agent, and protein-bound ICG exhibits fluorescence under near-infrared light illumination (750–810 nm) and retains the human protein structure [11]. In 2008, the first report on fluorescence during liver surgery described the use of ICG to identify liver segments. [12] [12] In the past 13 years, significant advances in this field have been made, including liver segment visualization [13,14], hepatobiliary tumor visualization [15,16], cholangiographic visualization [17,18], and liver transplantation [19]. Large-scale literature databases currently impede quick and accurate searches of articles by clinicians and researchers. In addition, numerous publications in this field lack overall macrounderstanding and systematic research.

Bibliometric analysis uses techniques such as citation analysis to evaluate research performance over the past few decades and subsequently predict trends [20,21]. Since the publication of the first bibliometric paper in *JAMA* in 1987 by Garfield [22], a growing volume of research on bibliometrics has been conducted in various fields. However, no bibliometric studies have been reported on the application of ICG in hepatobiliary surgery. Thus, the research results in this field need to be summarized and analysed. This information may be valuable for the treatment plans and resource allocation of clinical doctors and management personnel. The present study provides a comprehensive and rapid overview of the publication status of ICG in hepatobiliary surgery by exploring the bibliometric characteristics of all authors, countries, institutions, journals, and keywords over the past 13 years.

## 2. Methods

### 2.1. Databases

Scientific publications were extracted from the SCI-E database in the Web of Science Core Collection.

### 2.2. Search terms

In the present study, the following retrieval terms were used: {[TS = hepat \* or choice \*]} or {[TS = live or hepatic or "bill duct" or gallbladder] and [TS = surgery or operation]} and [TS = ICG or "indocyanine green"], country/region = unlimited. The date range for document retrieval was from January 1, 2008, to December 31, 2021. The following conditions were restricted: the document types were articles, reviews, meeting abstracts, or letters, and the language was English or German. To prevent database updates from producing data deviations, documents were searched on January 7, 2022, in the present study.

### 2.3. Data analysis

We exported the full records of the search results in Excel tables and text, and the data were input into CiteSpace software to generate visual images [23]. The following visual images were included: the distribution and collaboration of the author/s/countries/regions/institutions, the distribution of the journals most influential, and the development status of the keywords.

### 2.4. Statistical analysis

The present study describes the current situation of the application of ICG in hepatobiliary surgery using objective data and discusses the changes in the past and future trends.

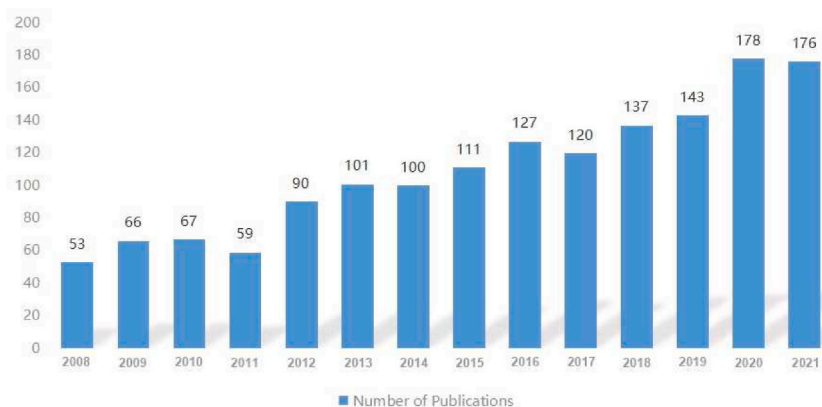


Fig. 1. Number of publications from 2008 to 2021.

### 3. Results

#### 3.1. Evolution over the period 2008–2021

The number of papers in a certain period reflects the developmental level of the research. We identified 1527 publications, including 1277 articles, 156 reviews, 68 meeting abstracts, and 27 letters in total. These publications were cited 30742 times, each paper was cited 20.12 times on average, and the h-index was 72 [24]. The number of publications presented a continuing upwards trend from 2008 to 2020. Fig. 1 was observed from 2008 to 2021.

#### 3.2. Countries/regions and funding analysis

The most frequently published articles came from 10 countries (Table 1), among which Japan published the most articles (31.09 %), followed by China (21.47 %), the USA (15.45 %), Germany (8.44 %), and South Korea (6.41 %). Similarly, the number of citations in Japan (9682) was greater than that in other countries, followed by the USA (7516) and China (5495). CiteSpace software was used to analyse the retrieved literature and generate a country/region visualization map. Fig. 2 shows the country/region cooperation network visualization map. The leading countries/regions have few connections with other countries, suggesting that these have independent research abilities. There was more cooperation between England and other countries/regions despite its general article publishing ability. The top 5 countries/regions with the most bursts were Germany (2008–2011), the Netherlands (2011–2013), Saudi Arabia (2013–2015), the Czech Republic (2008–2013), and Poland (2013–2015) (Fig. S1). These countries/regions may publish more articles in the future.

Table 2 shows the top 10 funding sources in this field. The number of China Natural Science Foundation (10.54 %) was the highest, followed by the National Institutes of Health (6 %) and the Department of Public Services of the U.S. Department of Health (6 %). Generally, sponsorship mainly comes from national governments.

#### 3.3. Authors and institutions analysis

A total of 7153 authors participated in the research in this field, and Kokudo N published the most papers (72). The most cited authors were Kokudo N (2857), Ishizawa T (2211), and Kiyoshi H (1668). Fig. 2 displays the author's cooperation network visualization map, which shows that there were a few links between various countries/regions of authors. The top number of publications was mainly from Japanese authors. The top 5 authors for counts of co-occurrence were Kokudo N (58), Hasegawa K (36), Ishizawa T (33), Kaneko J (22), and Sakamoto Y (22) (Table 3). Fig. 3 also shows that Kokudo N cooperates closely with Ishizawa T, who all come from the University of Tokyo. The 5 authors with the most bursts were Arita J (2015–2018), Tian Jie (2017–2021), Aoki T (2009–2015), Akamatsu N (2016–2019), and Sugawara (2013–2015) (Fig. S2).

The top institutions that published the most articles were the University of Tokyo (91, Japan), followed by the Chinese Academy of Sciences (34, China), Sun Yat-sen University (32, China), Kyoto University (24, Japan), and Kyushu University (23, Japan) (Table 4). The University of Tokyo ranked first in terms of the number of references (3108), followed by Leiden University (1909, England) and the Chinese Academy of Sciences (767). Fig. 4 shows various scientific research institutions that have many connections with each other. In addition, the 3 institutions with the strongest burst intensities in recent years were Amsterdam University (2011–2013), Showa University (2020–2021), and Zhejiang University (2020–2021) (Fig. S3).

#### 3.4. Journal analysis

In the present study, 461 journals were included, and the top 10 journals published a total of 310 articles, accounting for 20.29 % of the total number of journals; these journals published more than 20 articles (Table 5). The 3 most common journals were the Annals of Surgery (718), Hepatology (651), and British Journal of Surgery (560) (Fig. S4). The top 3 journals with the strongest burst intensities in recent years were intensive care medicine (2008–2012), clinical science (2008–2014) and critical care medicine (2008–2013) (Fig. S5).

**Table 1**

Top 10 countries/regions in terms of number of publications.

Rank	Countries/regions	The number of publications	The counts of citations	Percent of total publications in all countries
1	Japan	475	9682	31.086
2	China	328	5495	21.466
3	USA	236	7516	15.445
4	Germany	129	2683	8.442
5	South Korea	98	1489	6.414
6	France	76	1979	4.974
7	Italy	71	1432	4.647
8	Netherlands	65	3622	4.254
9	England	50	1111	3.272
10	Taiwan, China	45	1353	2.945



Fig. 2. Collaboration network maps of countries/regions.

**Table 2**

Top 10 funding sources in terms of number of supports.

Rank	Source of fundings	Number of grants	The percent of total fundings
1	National Natural Science Foundation of China Nsf	161	10.537
2	National Institutes of Health Nih USA	94	6.152
3	United States Department of Health Human Services	94	6.152
4	Ministry of Education Culture Sports Science and Technology Japan Mext	61	3.992
5	Nih National Cancer Institute Nci	61	3.992
6	Japan Society for The Promotion of Science	36	2.356
7	Grants in Aid for Scientific Research Kakenhi	27	1.767
8	European Commission	26	1.702
9	Nih National Institute of Biomedical Imaging Bioengineering Nibib	18	1.178
10	Ministry of Health Labour and Welfare Japan	17	1.113

**Table 3**

Top 10 authors in terms of number of publications.

Rank	Authors	The number of publications	Affiliated organization	The counts of citations
1	Norihiko Kokudo	72	Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo	2857
2	Kiyoshi Hasegawa	47	Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo	1668
3	Ishizawa Takeaki	44	Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo	2211
4	Aoki Taku	34	Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo	1333
5	Sakamoto Yoshihiro	31	University of Tokyo	710
6	Kaneko Junichi	29	Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo	981
7	Tian Jie	21	University of Chinese Academy of Sciences	646
8	Arita Junichi	20	Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo	365
9	Stockmann Martin	20	University Hospital Charite'	419
10	Yoshikuni K	19	Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, University of Tokyo	330

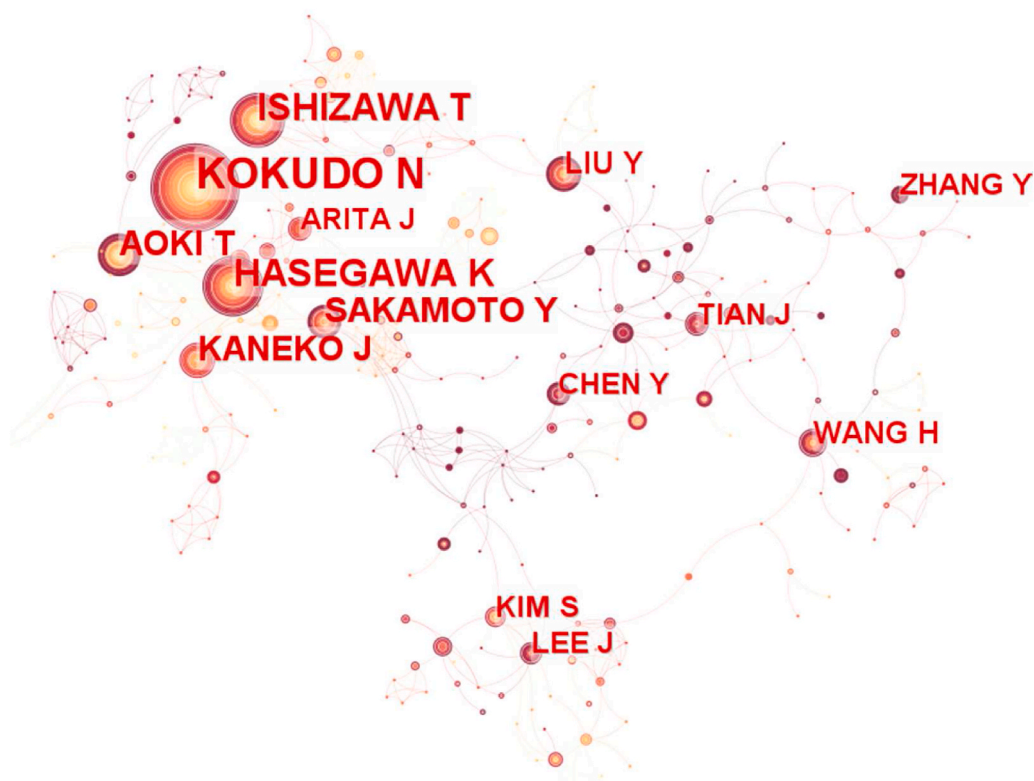


Fig. 3. Collaboration network maps of authors.

Table 4

Top 10 institutions in terms of number of institutions.

Rank	institutions	The number of publications	The counts of citations	Average number of references	The percent of total institutions
1	The University of Tokyo	91	3108	34.15	5.955
2	Chinese Academy of Sciences	34	767	22.56	2.225
3	Sun Yat-sen University	32	496	15.5	2.094
4	Kyoto University	24	418	17.42	1.571
5	Kyushu University	23	530	23.04	1.505
6	Seoul University	21	384	18.29	1.374
7	Sichuan University	21	162	7.71	1.374
8	NAGASAKI University	19	195	10.26	1.243
9	Leiden University	18	1909	106.06	1.178
10	Changgeng University	17	293	17.24	1.113

### 3.5. Co-cited references analysis

We explored the top 10 cocited references related to the cocited references. As presented in Tables 6 and 3 articles co-cited between 40 and 50 times, 6 articles co-cited between 30 and 40 times, and 1 article cocited between 20 and 30 times. Most recent studies have indicated that more attention has been given to the application of ICG in laparoscopic hepatobiliary surgery.

### 3.6. Spot spot analysis

Keyword co-occurrence analysis can reveal the hot spots of research, and high-frequency keywords represent the main research direction in this field. Co-occurrence analysis helped us to identify future study directions. CiteSpace software was used to construct a keyword co-occurrence map. The top 10 keywords (Fig. 5) in terms of frequency of occurrence were "indocyanine green", "hepatocellular carcinoma", "response", "surgery", "hepatology", "therapeutic response", "cancer", "transformation", "cirrhosis" and "survival". Fig. S6 shows the keyword cluster analysis from 2008 to 2021, which included 10 clusters. Fig. S7 shows the timeline view of the keywords. The top 20 keywords with the strongest bursts during the past 13 years are shown in Fig. S8. Keywords were mainly

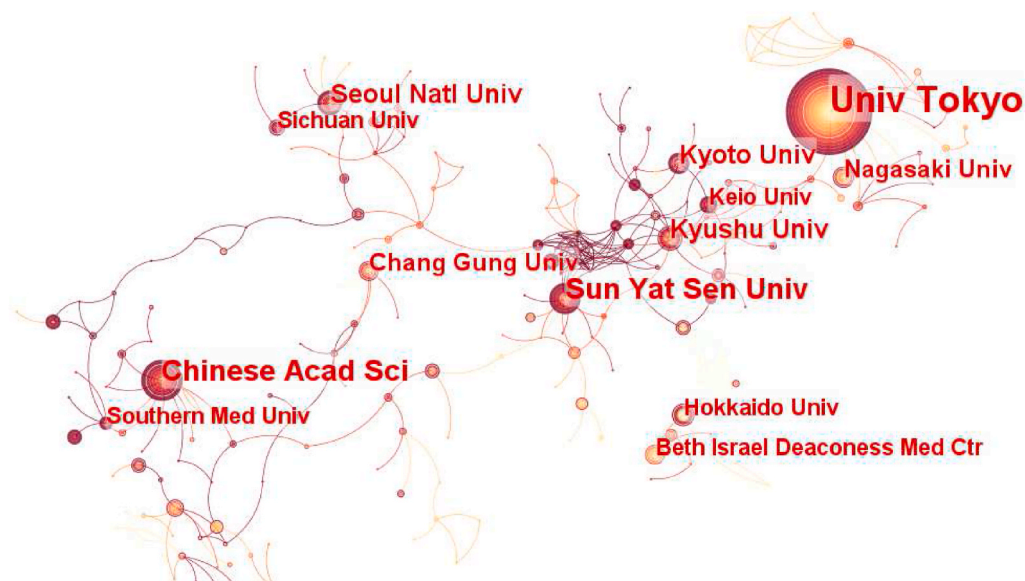


Fig. 4. Collaboration network maps of organizations.

Table 5

Top 10 journals in terms of number of publications.

Rank	Journals	The number of publications	The counts of citations	The percent of total journals
1	SURGICAL ENDOSCOPY AND OTHER INTERVENTIONAL TECHNIQUES	65	1473	4.254
2	JOURNAL OF HEPATO BILIARY PANCREATIC SCIENCES	35	614	2.291
3	ANNALS OF SURGICAL ONCOLOGY	34	794	2.225
4	WORLD JOURNAL OF SURGERY	34	734	2.225
5	JOURNAL OF GASTROINTESTINAL SURGERY	27	380	1.767
6	HEPATO GASTROENTEROLOGY	26	246	1.702
7	PLOS ONE	24	358	1.571
8	HPB	23	302	1.505
9	JOURNAL OF SURGICAL ONCOLOGY	21	1137	1.374
10	PEDIATRIC BLOOD CANCER	21	0	1.374

concentrated from 2008 to 2013, which was a significant period of rapid development and exploration in this field.

#### 4. Discussion

The present study conducted a bibliometric analysis of the global research results on the application of ICG in hepatobiliary surgery from 2008 to 2021. The study showed that the number of publications and the citation rate of the application of ICG in hepatobiliary surgery increased significantly after 2008 and exhibited a gradual upwards trend. The most frequently searched topics in this area were hepatectomy, bile duct resection, liver transplantation, and tumors. The present study analysed articles from multiple dimensions of a topic, revealing the comprehensive development in this field over the past years and predicting hotspots.

Japan has the largest number of published articles, followed by China and the United States. Although China ranks second in terms of the number of publications, it has a significantly lower number of citations than Japan and the United States. Moreover, its research quality and influence still need to be improved. Countries with higher centrality were located mainly in Europe, including Serbia, Switzerland, England, and Sweden; these countries play key roles in the application of ICG in hepatobiliary surgery. The amount of support provided by the National Natural Science Foundation of China was significantly greater than that provided by other funds. With China having the highest incidence rate of liver cancer, the Chinese government has provided sufficient attention and support to this field. Eight of the top 10 authors, ranked by the number of published articles, were Japanese, indicating that most of the research came from Japanese institutions. Kokudo N published the most articles in this field related to his having a constant collaborative team [25–28]. By analysing the cocited authors, we suggest using the mode of cooperation and communication between institutions and researchers to improve research quality. Tian Jie ranks seventh among the top 10 influential authors in this field, ranks first in China, and is one of the most promising researchers with the third-largest burst intensities in recent years.

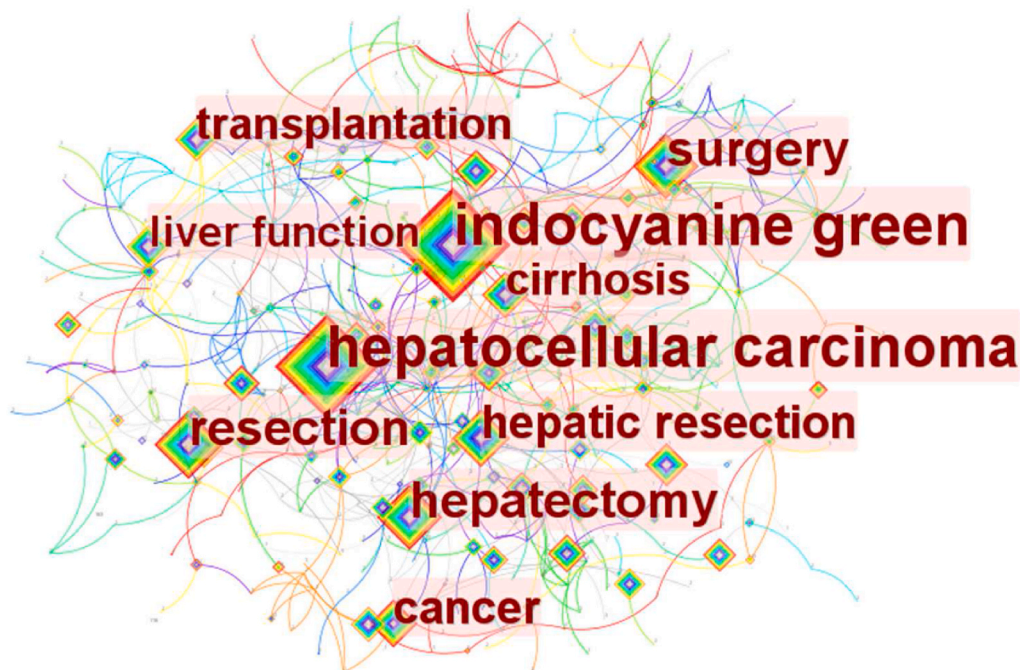
In 2020, Tian Jie et al. developed a near-infrared II multispectral imager with a spectral range of 400–1700 nm and completed 23



**Table 6**

Top 10 co-cited references in terms of the number of co-cited references.

Rank	the counts of cocited reference	Cocited reference	Author and year	Journals
1	42	Mechanistic Background and Clinical Applications of Indocyanine Green Fluorescence Imaging of Hepatocellular Carcinoma	Ishizawa T (2014)	ANN SURG ONCOL
2	42	Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy	Ishizawa T (2010)	BRIT J SURG
3	41	Near-Infrared Fluorescence-Guided Resection of Colorectal Liver Metastases	van der Vorst JR (2013)	CANCER-AM CANCER SOC
4	37	Applications of fusion-fluorescence imaging using indocyanine green in laparoscopic hepatectomy	Terasawa M (2017)	SURG ENDOSC
5	37	Clinical applications of indocyanine green (ICG) enhanced fluorescence in laparoscopic surgery	Boni L(2015)	SURG ENDOSC
6	37	Real-Time Identification of Liver Cancers by Using Indocyanine Green Fluorescent Imaging	Ishizawa T (2009)	CANCER-AM CANCER SOC
7	35	Real-time near-infrared (NIR) fluorescent cholangiography in single-site robotic cholecystectomy (SSRC): a single-institutional prospective study	Spinoglio G (2013)	SURG ENDOSC
8	32	Anatomical Liver Resections Guided by 3-Dimensional Parenchymal Staining Using Fusion Indocyanine Green Fluorescence Imaging	Inoue Y(2015)	ANN SURG
9	31	Optimization of near-infrared fluorescence cholangiography for open and laparoscopic surgery	Verbeek FPR (2014)	SURG ENDOSC
10	29	Near-infrared fluorescent cholangiography facilitates identification of biliary anatomy during laparoscopic cholecystectomy	Osayi SN(2015)	SURG ENDOSC

**Fig. 5.** Keyword frequency graph.

ICG fluorescence-guided liver tumor operations [29]. The research results were reported in the top journal, *Nature Biomedical Engineering*, indicating that China has gradually shifted from the exploration stage of ICG application to the research and development stage of large-scale medical equipment. The analysis revealed that the top 10 institutions with the most published articles were in Japan, China, South Korea, the Netherlands, and Taiwan. Among them, four institutions were in China, but the number of citations was considerably lower than that of the University of Tokyo, which was the university that published the most articles. This discrepancy suggests that the quality and influence of Chinese research need to be improved. The collaborative visualization map shows that 9 of the 10 cooperative institutions belong to Japan, which may be related to the strong independent research capabilities of the Japanese people and their enormous scientific research team. Showa University (2020–2021) and Zhejiang University (2020–2021) have exhibited increased burst intensities in recent years, indicating that they are the most promising institutions for the future.

Among the top 10 journals, *Surgical Endoscopy and Other Interventional Techniques* had the largest number of published articles and

was the most frequently cited; the *Journal of Hepato Biliary Pancreatic Sciences* was the journal with the highest impact factor. Seven of the top 10 journals were in the field of oncology surgery, two of which were in the field of hepatobiliary surgery. The reason may be that professional surgery journals receive fewer articles than general surgery journals. Compared with other journals, *Annals of Surgery* had the highest frequency of cocitations (718). *Intensive Care Medicine* (2008–2012) had the highest burst intensity (16.84), which we suggest being given continued attention.

A number of cocited literature reviews can reveal important theories of ICG application in hepatobiliary surgery. The highest number of cocited articles indicates that the mechanism and background of ICG have received increased amounts of research attention in recent years. Takeaki Ishizawa [30] indicated that Na (+)/taurocholate cotransporting polypeptide and organic anion transporter polypeptide 8 facilitated the uptake and accumulation of ICG in liver cancer (NO.1). Takeaki Ishizawa [28] comprehensively described ICG fluorescence angiography, which identifies the anatomical structure of the biliary tract. In addition, the application of ICG in laparoscopic surgery [31], [-34] tumor identification [35], and liver metastasis [36] has also been a research focus. These studies are cited frequently and are regarded as the basis of this field.

Keywords are considered the main topics of a field over a certain period. In the present study, we labelled topics into clusters and chronological phases and identified topic clusters. We further identified the hottest topics by keyword analysis and found that keywords such as “indocyanine green” and “hepatocellular carcinoma” were thus far the most frequently used keywords, followed by “resection,” “surgery,” “hepatectomy,” “hepatic resection,” “cancer,” “transplantation,” “cirrhosis,” and “survival.” ICG clearly provides advantages in the localization of liver segments and liver lesions in hepatobiliary surgery. According to the keyword timeline, the main hot topics were “indocyanine green” and “anatomical hepatic resection” from 2008 to 2010. Aoki T [12] used the infrared observation camera system PDE-2 to determine whether the liver segment and subsegment were demarcated after ICG was injected into the portal vein. The present study demonstrated that near-infrared fluorescence imaging is a novel and reliable technique for identifying hepatic segments and subsegments for anatomical hepatectomy. The main hot topics were “indocyanine green,” “biliary anatomy,” “laparoscopic cholangiectomy,” and “hepatectomy” during the 2011–2019 period. These studies focused on the intraoperative safety and mechanistic background of ICG. Yosuke Inoue et al. [37] indicated that ICG fluorescence imaging was a safe imaging technique for anatomical liver resection and provided 3-dimensional visualization of demarcations compared with traditional demarcation techniques. This article was published in the international top journal *Annals of Surgery* and confirmed the safety of ICG fluorescence imaging in hepatectomy patients. Takeaki Ishizawa et al. [30] determined the mechanism allowing the identification of HCC by intraoperative ICG fluorescence imaging. Muga Terasawa et al. [38] confirmed the safety of ICG in laparoscopic hepatectomy. With increasing research in liver transplantation (LT) in recent years, the main keywords gradually focused on “liver transplantation” and “probe” during the 2020–2021 period. Damien Dousse et al. [39] successfully used fluorescence quantification of grafts to assess 3-month liver survival during LT. Rodrigo Figueroa et al. [40] [40] indicated that primary graft dysfunction could be related to ICG; Vahrmeijer AL et al. [41] translated the novel fluorescent probe SGM-101, whose nonspecificity helps reduce false-positive cancer. Currently, the efficacy of SGM-101 has been verified by animal experiments, and phase III studies are still in the recruitment stage. That is, specific probes and equipment can increase the accuracy of operation. In recent years, the da Vinci robotic platform has been widely used as the hottest research topic in surgery. In 2017, A Gangemi et al. [42] performed at the University of Illinois at Chicago (UIC) Division of General, Minimally Invasive and Robotic Surveillance retrospectively 676 ICG-treated robotic cholecystomies (ICG-treated RC). Finally, due to the sample size variability and the non-randomized nature of this study, it was unknown that robot surgery may significantly increase the rate of open conversion in both acute and non-acute settings.

Overall, ICG has gradually played an important role in perioperative management. The application of ICG in LT and cancer-targeted fluorescence molecular imaging still requires a pilot study. Timeline visualization maps showing that liver function is related to recovery and protection [43,44] may be a trend of future research. Our research shows that the application of the ICG in determining LT survival and prognosis is currently the main research focus, and we anticipate breakthroughs in this field soon.

Cluster analysis revealed that 6 of the 10 clusters were related mainly to hepatobiliary surgery. The cluster also included postoperative complications and postoperative liver failure, in addition to hepatectomy and cholangiectomy. The timeline visualization map shows “recovery” and “protection,” which may be the trends of future research. The current study identified hepatectomy, choledochectomy, transplantation, and cancer as frequently used keywords in all studied periods from 2008 to 2020. The application of the ICG in determining LT survival and prognostic assessment was the primary research focus in 2021. The exploration of the application of ICG in LT is expected to be a hot research topic, and we believe that breakthroughs in this field can be made quickly.

This study has several limitations. First, only the core database in the WoS was chosen for this study because of its high-quality publications; however, a few articles might have been excluded from this analysis. Second, languages were limited from English to German, and studies in other languages were not included. The articles in the WoS core database are constantly updated, rendering our findings temporary. Finally, approximately 2 years have passed since the completion of this study, and some newly discovered studies have not been included. We will further expand and refine our research in the future.

## 5. Conclusions

The largest number of publications on the use of ICG in hepatobiliary surgery have been published in Japan. The University of Tokyo contributed the largest number of publications and citations in this field. The main research topics focused on hepatectomy, choledochectomy, liver transplantation, and cancer. The research frontier may focus on the application of ICG in LT. This study has important implications for researchers and doctors and provides a new perspective for the application of ICG in hepatobiliary surgery.



## Ethics declarations

Review and approval by an ethics committee were not needed for this study because this study did not involve animal or human experiments.

## Data availability statement

We agree that our study was deposited into a publicly available repository.

## CRedit authorship contribution statement

**Donglun Li:** Writing – original draft, Software. **Yue Hu:** Writing – original draft, Software. **Maoji Kang:** Formal analysis, Data curation. **Cheng Fang:** Writing – review & editing, Formal analysis. **Yu Gan:** Formal analysis, Data curation. **Xiaoli Yang:** Data curation. **Fangyi Peng:** Data curation. **Bo Li:** Visualization. **Jiali Wu:** Writing – review & editing, Conceptualization. **Song Su:** Writing – review & editing, Visualization, Resources.

## Declaration of competing interest

The authors have no conflicts of interest to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e31989>.

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