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DATABASE ANALYSIS

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Bibliometric Analysis of Pediatric Liver Transplantation Research in PubMed from 2014 to 2018

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Background: Pediatric liver transplantation is used to treat children with end-stage liver disease. This study explored the research hotspots and bibliometric characteristics of pediatric liver transplantation through a variety of bibliometric analysis software. We conducted hotspot analysis to help determine important directions for future scientific research.

Material/Methods: The study samples were articles related to pediatric liver transplantation published in PubMed in the past 5 years. The high-frequency keywords are extracted by BICOMB software, and then a binary matrix and a common word matrix were constructed. Gcluto software was used to perform double-clustering and visual analysis on high-frequency words, and then we obtained hot area classification. Strategic coordinates are constructed using Excel. Citespace and VOSviewer software are used for further analysis and bibliometric data visualization.

Results: A total of 36 high-frequency words were found in the 4118 studies. A peak map was drawn through double-cluster analysis. Biclustering analysis was used to calculate the concentricity and density of each hotspot. We obtained the top 10 countries/regions engaged in pediatric liver transplantation research. VOSviewer was used to visualize the co-author map.

Conclusions: We found 5 clusters and 7 aspects for pediatric liver transplantation. Additionally, calculation results showed that post-transplant lymphoproliferative disorder in pediatric patients and outcomes of multivisceral transplantation seem very promising. This conclusion is of great value for future exploratory research.

MeSH Keywords: Bibliometrics • Liver Transplantation • Pediatrics

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Background

Liver transplantation is the most effective method to treat pediatric end-stage liver diseases. In 1963, Thomas Starzl performed world's first liver transplant on a 3-year-old child with biliary atresia [1]. With the development of scientific technology, pediatric liver transplantation has been continuously improved in terms of surgical techniques, anesthesia management, donor liver access and preservation, immunosuppression, and management of postoperative complications. Pediatric liver transplantation has greatly evolved in recent decades [2,3], but problems still exist. For example, many parents of children have inadequate understanding of surgery, there are various limiting economic and social factors and difficulties in surgery, and these problems slow the development of the pediatric liver transplantation and contribute to the lack of continuity and efficiency.

Bibliometric analysis is a research method which uses mathematical or statistical methods to describe the quantity of external features of a document, and then evaluates and predicts the status and development trends of science and technology [4,5]. Bibliometric analysis focuses on the metrological characteristics of a large number of articles published in a certain field through a quantitative method [6]; it is an emerging discipline that studies the mathematical laws in the literature. With the continuous development of science and technology, the theories and methods of bibliometric have gradually been applied in various fields. Co-word analysis is an important method of bibliometrics, and is widely used in China and abroad. It can be used to identify the trend of topics and hot topics [7]. The principle is that, when 2 terms that can express the research theme and research direction of a certain subject area appear in the same document, it shows that there is a certain inherent relationship between the 2 words, and with more occurrences, there are shorter distances and closer relationships. The use of modern statistical technology to classify the keywords of the disciplines to summarize the research hotspots and research structure of the discipline has important reference value for planning the discipline layout and adjusting the discipline direction [8–11]. Bibliometric research often uses software (such as Citespace, Vosviewer, BICOMB, and Excel) for visual analysis.

Many papers related to pediatric liver transplantation have been published in the past decade, and one study analyzed the bibliometric focus on pediatric liver transplantation from 1945 to 2014. However, few studies have been conducted to analyze the publication data in a systematic way in the last 5 years. In this study, we performed a bibliometric analysis of articles on pediatric liver transplantation in PubMed from 2014 to 2018 using various analytical tools to explore the research trend and hotspots.

Material and Methods

Data collection

Data were obtained from the PubMed database, which allows searching for published medical articles through a search engine provided by the National Biotechnology Information Center in the United States. Its database source is MEDLINE. Its core theme is medicine, but it also covers other areas related to medicine. We obtained studies on pediatric liver transplantation or child liver transplantation in PubMed from January 1, 2014 to December 31, 2018, for English-language articles only. The search strategy was: ("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields]) AND "liver transplantation"[MeSH Terms]) OR ("child"[MeSH Terms] OR "child"[All Fields]) AND "liver transplantation"[MeSH Terms]) AND ("2014/01/01"[PDAT]: "2018/12/31"[PDAT]). The research identified 4118 articles in PubMed. And title, author, country, institution, MeSH terms, and year of publication were contained as key qualifications, which were saved as XML formats.

Data extraction and analysis

Bibliographic Items Co-occurrence Matrix Builder (BICOMB) is used for data extraction and matrix construction. This software is a more commonly used bibliometrics software for keyword co-occurrence and was designed by Professor Lei Cui of China Medical University [12]. After data extraction, we obtained the most common major MeSH terms, as shown in Table 1. The source studies at high frequencies and the major MeSH terms were shown be referring to bilinguals. The binary matrix was output with the source literature as rows and high-frequency subject terms as columns. To better show the clustering results, we use Gcluto for double-cluster analysis, which was developed by Rasmussen and Karypis of the University of Minnesota to perform double-cluster analysis on the MeSH terms-source article matrix [13]. External similarity (ESim) represents the average similarity between clusters, and internal similarity (ISim) represents the average similarity within a cluster. The ESim and the ISim were used to optimize the results. We double-clustered the binary matrix and obtained the hotspot categories through Gcluto software, then we generated visual mountain maps and heat maps based on the results of cluster analysis. Semantic relationships between the MeSH terms and the content of each study in different groups were assessed.

Vosviewer, a freely available computer software for bibliometric data construction and visualization [14], was used for high-frequency terms and to create a keyword density map. CiteSpace is software for identifying and displaying new trends and new developments in scientific literature, and it was developed by Chaomei Chen in 2004 [15–17]. CiteSpace was usually used to assess the productivity of authors, countries, and

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Table 1. High-frequency major MeSH terms from the included publications on pediatric liver transplantation.

Rank	Keywords	Frequency	Percentage (%)	Cumulative percentage (%)
1	Humans	3565	5.2213	5.2213
2	Female	2511	3.6776	8.8989
3	Male	2501	3.6630	12.5619
4	Child	1895	2.7754	15.3373
5	Child, Preschool	1357	1.9875	17.3248
6	Adolescent	1333	1.9523	19.2771
7	Adult	1211	1.7736	21.0507
8	Infant	1138	1.6667	22.7174
9	Middle-Aged	1073	1.5715	24.2889
10	Retrospective Studies	1070	1.5671	25.8561
11	Liver Transplantation	1038	1.5203	27.3763
12	Treatment Outcome	1025	1.5012	28.8775
13	Young Adult	753	1.1028	29.9804
14	Aged	629	0.9212	30.9016
15	Risk Factors	593	0.8685	31.7701
16	Liver Transplantation/Adverse Effects	583	0.8539	32.6240
17	Liver Transplantation/Methods	507	0.7426	33.3665
18	Follow-Up Studies	449	0.6576	34.0241
19	Time Factors	409	0.5990	34.6232
20	Living Donors	405	0.5932	35.2163
21	Animals	370	0.5419	35.7582
22	Infant, Newborn	356	0.5214	36.2796
23	Prognosis	355	0.5199	36.7996
24	Graft Survival	307	0.4496	37.2492
25	Liver/Pathology	288	0.4218	37.6710
26	Liver Transplantation/Mortality	243	0.3559	38.0269
27	Prospective Studies	226	0.3310	38.3579
28	Survival Rate	223	0.3266	38.6845
29	Severity of Illness Index	219	0.3207	39.0052
30	Age Factors	217	0.3178	39.3231
31	End-Stage Liver Disease/Surgery	209	0.3061	39.6292
32	Incidence	192	0.2812	39.9104
33	Liver Neoplasms/Surgery	189	0.2768	40.1872
34	Liver Neoplasms/Pathology	187	0.2739	40.4611
35	Biliary Atresia/Surgery	183	0.2680	40.7291
36	Immunosuppressive Agents/Therapeutic Use	180	0.2636	40.9927

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Table 2. The centrality and density of the 5 clusters.

Cluster	Intra-class link averages	Density-Y	Inter-class link averages	Centrality-X
0	88.2	31.37	191.0	99.02
1	17.0	–41.03	24.3	–65.46
2	61.0	2.99	34.6	–55.61
3	50.75	–6.9	60.25	–29.07
4	70.8	13.42	139.0	51.11
Average	57.55		89.83	

institutions, and to determine international cooperation and geographical distribution, so that research hotspots in specific areas can be explored.

Strategic coordinate

We used Excel to import the clustering information of gCLUTO into the co-word matrix, calculated the average value of intra-class links and the average value of inter-class links, and then calculated the concentricity and density (Table 2). In the strategy diagram, the X axis is set to the degree of concentricity, which indicates the strength of the cluster's interaction with external categories. The concentricity of a category is calculated by the strength of the connection between the high-frequency words of that category and the high-frequency words of other categories. The Y axis represents density, which shows the strength of internal integrity for a given category. The density of a category is calculated from the average link in the category [18–21].

Results

Figure 1 shows the numbers of articles published in PubMed about pediatric liver transplantation studies from January 1, 2014 to December 31, 2018. The high-frequency keywords in pediatric liver transplantation were generated by Vosviewer to achieve overlay visualization (Figure 2). Different colors represent the corresponding publication time. Based on the high-frequency words, a binary matrix was constructed, the frequency number before the 36th word is greater than its ordinal number, and the frequency number of the high-frequency term after the 37th word is less than its ordinal number. Thus, the terms ranked higher than 36th can be defined as very high-frequency. There were 36 high-frequency major MeSH terms from the included publications on pediatric liver transplantation (Table 1). The major MeSH terms appear as a row and the PubMed Unique Identifiers of source articles appear as a column based on the co-occurrence of high-frequency MeSH terms in the same article. We constructed a high-frequency major MeSH terms-source articles matrix. In the matrix, "1" means

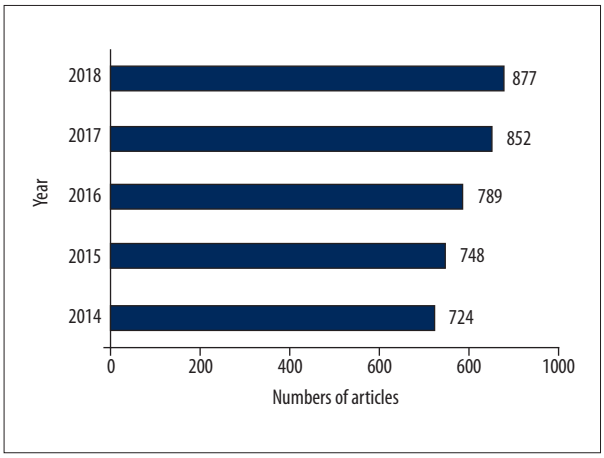

Figure 1. Numbers of articles published about pediatric liver transplantation in last 5 years.

that the term is present in the article, and "0" indicates that it is not present. Then, a matrix of co-words was established. In that matrix, the numbers indicate the numbers of co-occurrences between 2 terms.

Different numbers of clusters were used for double-cluster analysis. In Figure 3A, each category is numbered from 0 to 4. In mountain peak visualization, by using the multidimensional scaling method to determine the location of each cluster center, it is possible to quickly determine the main clusters and to assess similarity between clusters. The shape of each cluster is represented by a Gaussian curve, which is used to estimate the distribution of the data in each cluster. Each mountain peak is a cluster, and the information of the group is displayed by the position, volume, height, and color of the peaks. The volume of a mountain peak is proportional to the number of studies contained in the group. The larger the volume, the greater the number of articles. The height of the peaks is proportional to the intra-class similarity. The greater the intra-class similarity, the steeper the mountain. The peaks with the highest intra-class similarity are red. Only the display at the peak of the mountain is significant, and the other positions have been smoothed. Figure 3B shows a visualized matrix of the biclustering of high-frequency keywords of pediatric liver transplantation. Each row

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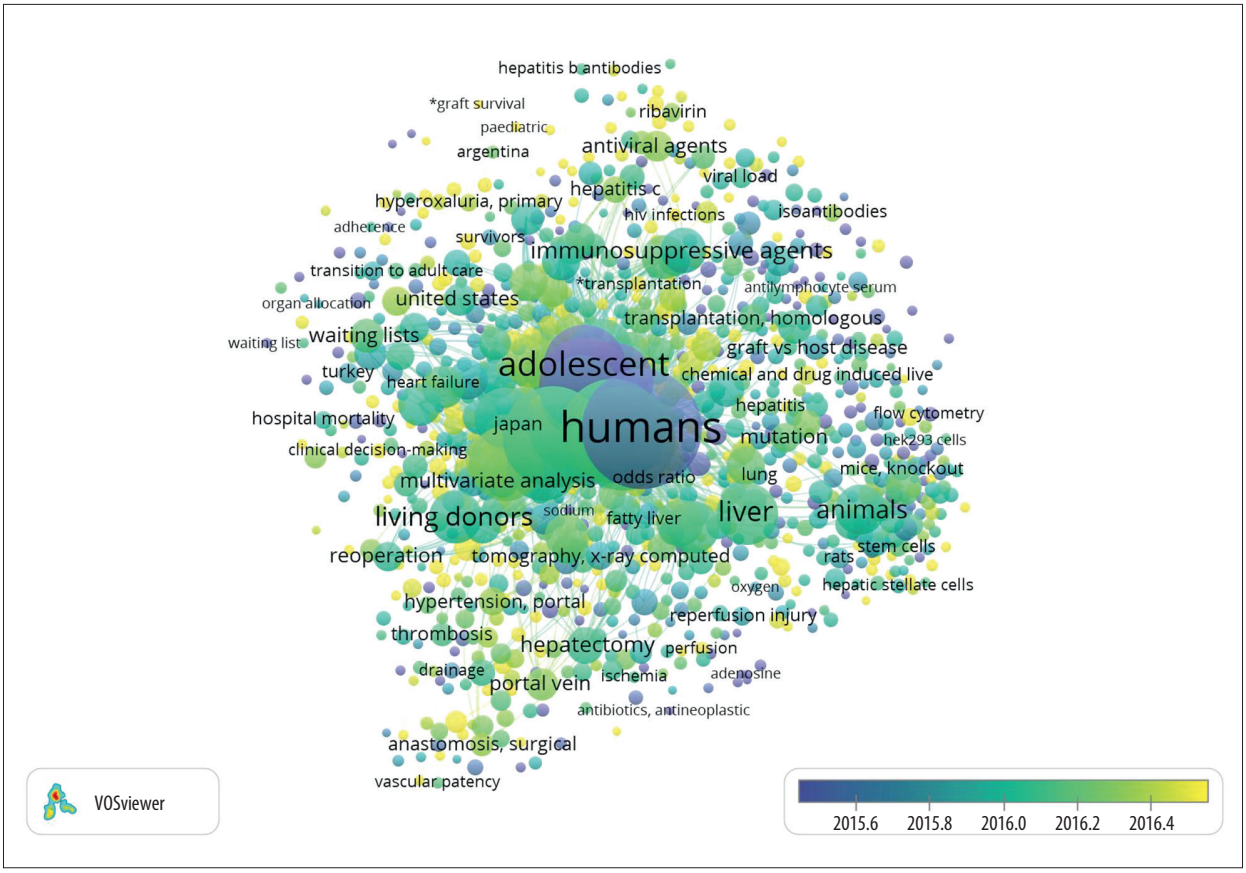

Figure 2. High-frequency keyword overlay visualization by Vosviewer.

represents a high-frequency keyword, and each column represents an article. The red color in the matrix indicates that the high-frequency word appears in the corresponding article. A larger value shows as a deeper red grid, white represents a value closer to zero, and negative values are green. The double-clustering matrix visualization showed that 36 major MeSH terms were totally clustered in 5 peaks. The hierarchical tree on the left describe the keyword clustering results, and the hierarchical tree on the top show the article clustering results. The colors in the figure indicated whether keywords appeared. By summarizing the semantic relationship between high-frequency words and source articles, we summarized the research on pediatric liver transplantation into 7 hot topics.

1. Critical elements in pediatric allograft selection (Cluster 0);
2. Surgical treatment for childhood hepatoblastoma (Cluster 0);
3. Post-transplant lymphoproliferative disorder in pediatric patients (Cluster 1);
4. Results and improved outcomes in pediatric liver transplantation (Cluster 2);
5. Fibroadenoma after living donor liver transplantation (Cluster 2);
6. Outcomes of multivisceral transplantation (Cluster 3);
7. Food allergies developing after solid organ transplant (Cluster 4).

The strategic coordinate chart shows the centrality with the X axis and the density with the Y axis. Clusters in the first quadrant have high centrality and density. Clusters in this quadrant are highly developed and important topics in the subject area. Clusters in the second quadrant have a high degree of development and a very professional and peripheral theme, which is very important in terms of the field itself. Clusters in the third quadrant are low-density and low-centrality, which mainly represent emerging themes. Clusters in the fourth quadrant are important for the research area, but have not yet been developed. As can be seen in Figure 4, clusters 0 and 4 are in the first quadrant, representing the corresponding categories in the central and core field. Cluster 2 is in the second quadrant, representing the corresponding category is in a peripheral mature domain. Clusters 1 and 3 are in the third quadrant, indicating that their corresponding categories are in relatively unpopular fields (Figure 4).

Network of co-authors' countries and institutions are shown in Figure 5A. We found that the USA had the most publications (1323) of studies according to the top 10 list of countries/regions (Table 3) which were engaged in the study of pediatric liver transplantation, followed by Japan (456), and Italy (340). The network map of departments involved in pediatric liver

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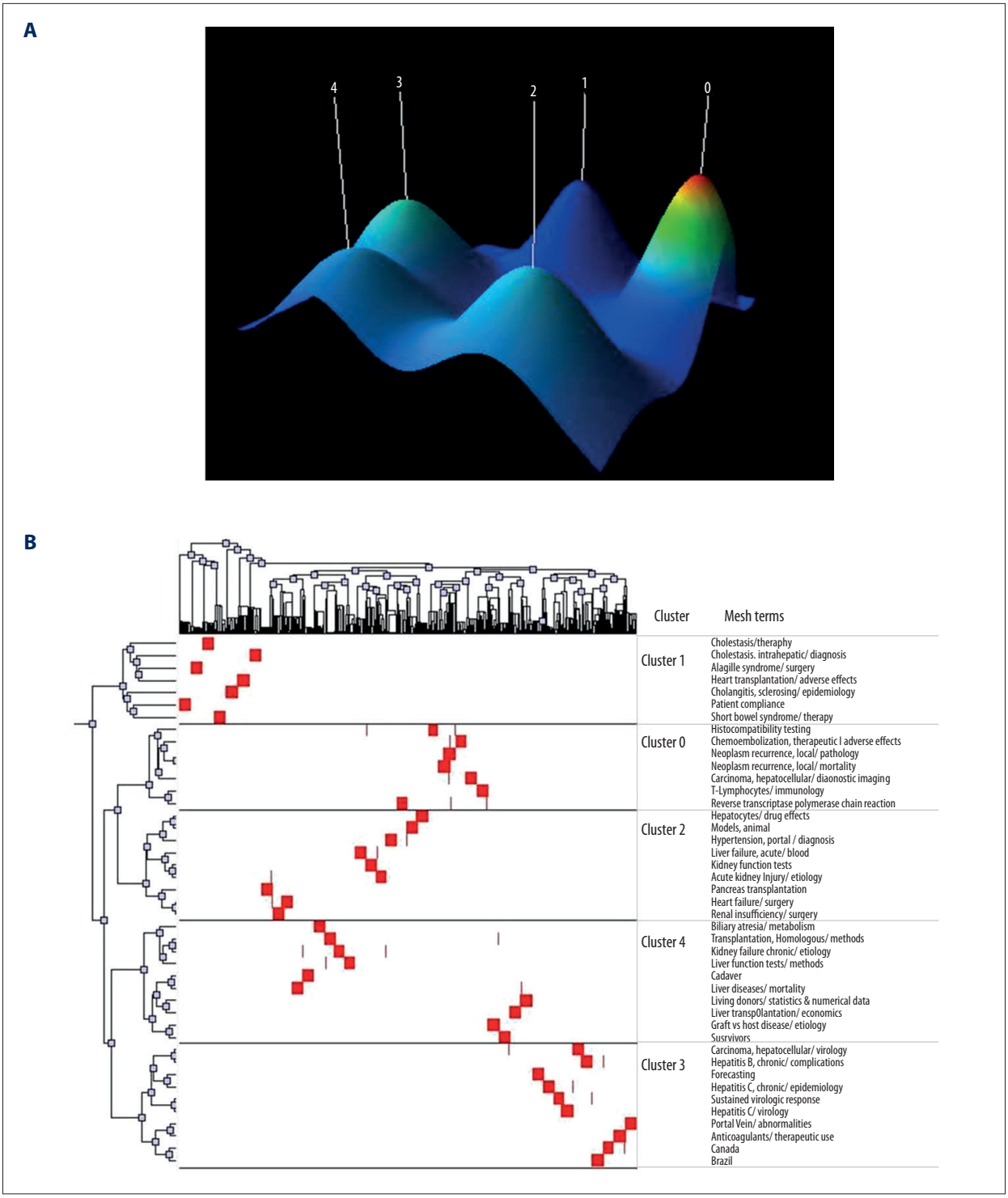

Figure 3. (**A**) Mountain visualization of biclustering of highly frequent keyword of pediatric liver transplantation. (**B**) Visualized matrix of the biclustering of high-frequency keywords of pediatric liver transplantation.

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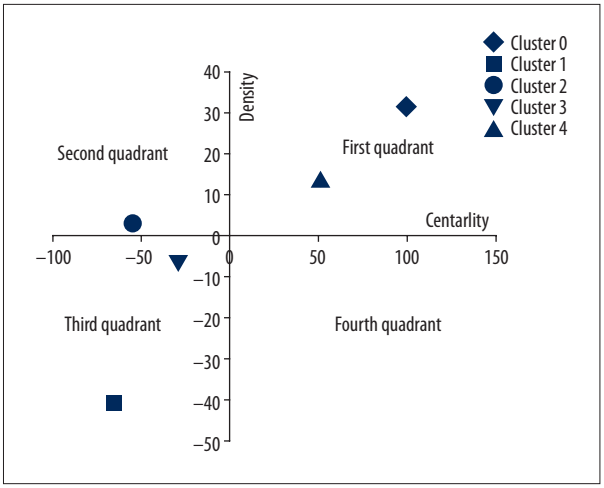

Figure 4. Strategic diagram of clusters.

transplantations is shown in Figure 5B. The top 10 institutes in Table 3 contributed the great majority of the total publications. In this list, Department of Pediatrics ranked first, followed by Department of Surgery, Department of Pathology, and Department of Pediatrics Surgery.

Figure 6 shows the co-author map visualized by VOSviewer. Among these contributing authors, Kasahara Mureo and Inomata Yukihiro were the most active authors and researchers in this field. Table 4 indicates the rank of journals that published articles on pediatric liver transplantation in PubMed during 2014–2018. *Pediatric Transplantation* published the most articles in this research field (354), followed by *Liver Transplantation* (190), *Transplantation proceedings* (169), and *Journal of Pediatric Gastroenterology and Nutrition* (127). This table shows that these journals are influential sources of knowledge in pediatric liver transplantation.

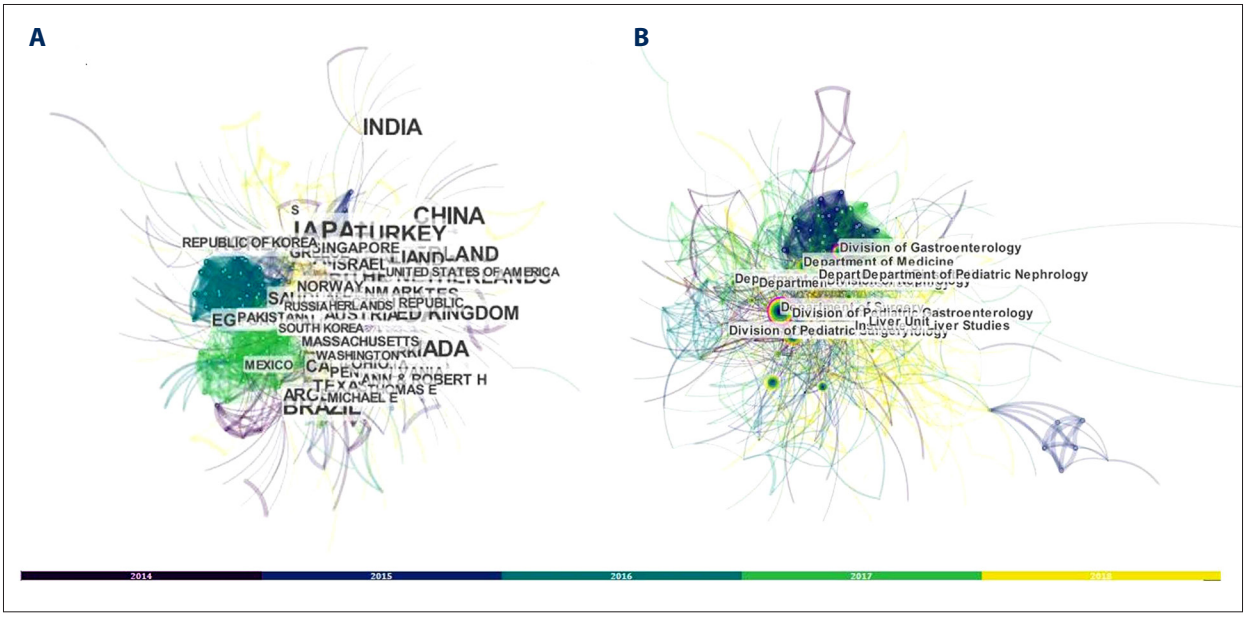

Figure 5. (**A, B**) Network of co-authors' countries and departments.

Table 3. The top 10 countries and institutes that contributed to publication in pediatric liver transplantation.

Rank	Country	Count	Institute	Count
1	USA	1323	Department of Pediatrics	546
2	Japan	456	Department of Surgery	437
3	Italy	340	Department of Pathology	228
4	Germany	317	Department of Pediatrics Surgery	180
5	China	284	Department of Radiology	176
6	France	209	Department of Gastroenterology	159
7	India	207	Division of Gastroenterology	144
8	Turkey	186	Department of Medicine	134
9	Brazil	179	Department of Internal Medicine	96
10	Canada	173	Department of Gastroenterology and Hepatology	87

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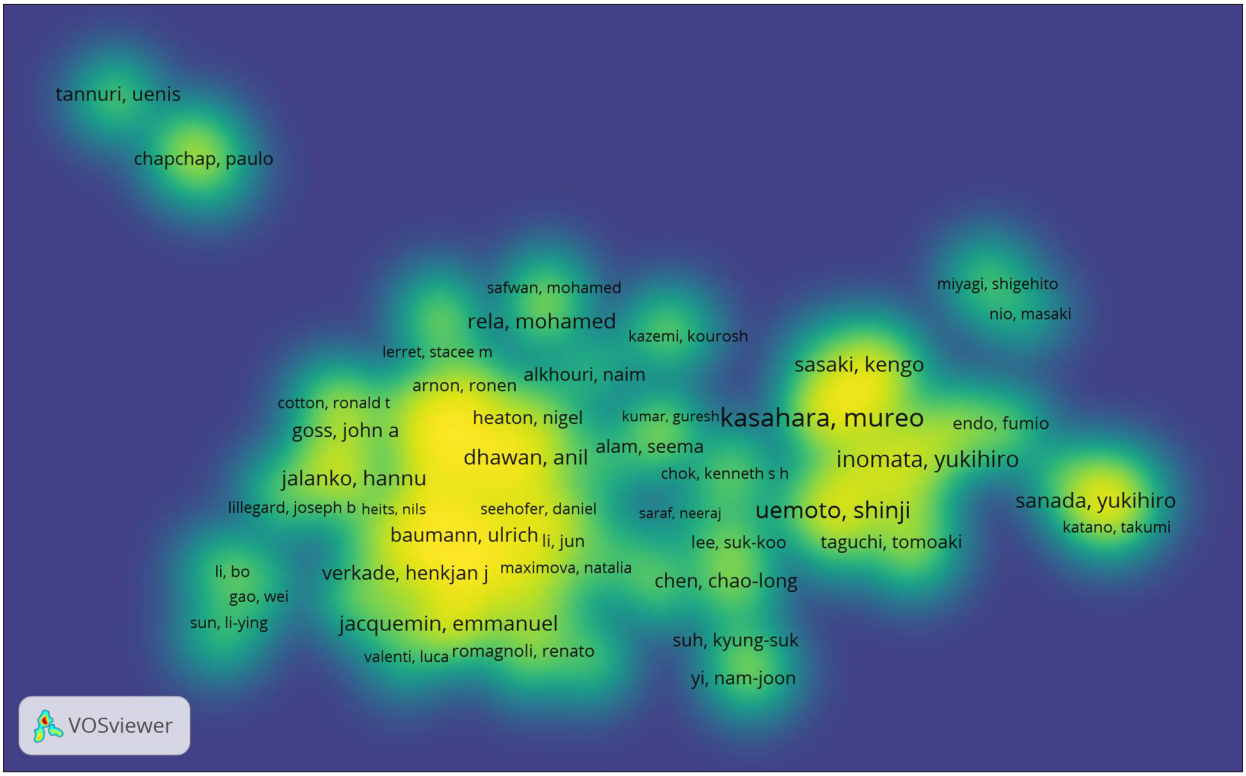

Figure 6. Co-author density map by Vosviewer.

Table 4. Rank of journals that published articles on pediatric liver transplantation in NCBI-PubMed during 2014–2018.

Rank	Journal title	Count (%)
1	Pediatric Transplantation	354 (8.6)
2	Liver Transplantation	190 (4.6)
3	Transplantation Proceedings	169 (4.1)
4	Journal of Pediatric Gastroenterology and Nutrition	127 (3.2)
5	Experimental and Clinical Transplantation	96 (2.3)
6	American Journal of Transplantation	86 (2.1)
7	Transplantation	75 (1.8)
8	World Journal of Gastroenterology	66 (1.6)
9	PLoS One	61 (1.5)
10	Journal of Pediatric Surgery	54 (1.3)
11	Hepatology	51 (1.2)
12	Annals of Transplantation	49 (1.2)
13	Clinical Transplantation	39 (1.0)
14	Liver International	37 (0.9)
15	Journal of Hepatology	35 (0.9)

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Discussion

Liver transplantation has become a routine treatment for end-stage liver disease in children. Indications and contraindications for liver transplantation are worthy of attention and analysis. The clinical treatment of pediatric liver transplantation has been fully discussed in the published literature, however, there was few of bibliometric studies on pediatric liver transplantation.

The present bibliometric study identified hot research topics, and we analyzed the status of their contents. Pediatric allografts are selected for optimal waiting for mortality and long-term survival. Currently, pediatric liver waiting list mortality is a serious problem, especially for young children [22]. Anatomy, graft volume, portal hypertension degree, and underlying disease are important considerations for selecting the best graft in children [22]. In the past 40 years, based on the increase in anatomical knowledge and the increasing experience in liver resection and the continuous updating of surgical techniques, the surgical operation of pediatric liver tumors has also progressed. Childhood hepatoblastoma is a malignant tumor of the liver that arises from the germinal tissue of the liver. Childhood hepatoblastoma mostly occurs in infants and young children. Surgical treatment of hepatoblastoma in children is directly related to the prognosis of the child. In transplant patients, calcineurin inhibitors inhibit T cells to reduce the regulation of B cell proliferation, in which case they are easily infected with Epstein-Barr virus. B lymphocyte hyperplasia eventually developed into lymphoproliferative disease after transplantation. PTLD is a serious complication of solid organ transplantation in children, with a mortality rate of about 30% to 60%. Its incidence has increased over the past decade [23,24]. Multivisceral transplantation refers to the transplantation of 3 or more organs – liver-pancreas, duodenum, stomach, and small intestine – with or without the right hemicolon, and some include kidneys. Some new surgical methods such as liver-intestinal, liver-kidney, pancreas-kidney and multivisceral cluster transplantation have emerged recently. These new advanced surgical approaches improve the curative effect of abdominal organ transplantation. Food allergy is a morbidity occurring after solid organ transplantation, and it is very important to identify food allergy after transplantation, because food allergy may be life-threatening, leading to serious morbidity and thus affecting the quality of life of patients. More research is needed to report food allergies after solid organ transplantation, especially epidemiology, and relevant mechanisms should be proposed to guide clinical practice [25].

Pediatric liver transplantation has made remarkable achievements, has become a standardized treatment, and has brought hope for long-term survival to many children with end-stage liver disease. The further development of pediatric liver transplantation requires the joint efforts of multiple disciplines. Recent studies have found that the development of pediatric liver transplantation can be promoted through multiple links and multiple approaches, including establishing a well-functioning organ distribution network, improving surgical methods to reduce complications, improving short-term survival rates, and establishing a mechanism for multi-disciplinary collaboration. Liver transplantation for liver malignancies, especially hepatoblastoma, is a key development area [26], which is consistent with the research hotspots shown in this study.

From this study, we obtained high-frequency topic words of pediatric or child liver transplantation. From these high-frequency words, we can understand the hotspots of this research. Through double-cluster analysis, we obtained a peak map. The concentricity and density of each hot spot were calculated using the common word matrix and double-cluster analysis. We built mountain visualization and visualized matrix of the biclustering of high-frequency keywords in pediatric liver transplantation through software. Through the construction of the knowledge network, we learned which countries, institutes, and researchers are more active in pediatric liver transplantation. We assessed the rank of journals that published the most articles on pediatric liver transplantation, which accounted for about 36% of articles in this research area. In the strategic coordinate chart, the X axis represents the centripetal degree, which indicates the strength of the mutual influence, and is calculated by the strength of the connection between the high-frequency topic words in this category and the high-frequency topic words in other categories; The Y axis represents density, which indicates the strength of the internal integrity of a given category, and the density of a category is calculated from the average link in the category. Cluster 0 and cluster 4 were found in the first quadrant, which described surgical treatment for childhood hepatoblastoma and critical elements in pediatric allograft selection, and food allergies developing after solid organ transplant. Clusters located in this quadrant are important research topics and hotspots of their disciplines, and they have received more attention. Clusters located in the second quadrant had a high density, but centrality was low, which indicated that these research topics were closely related and have been well researched on their own, forming relatively independent research areas, but these research topics are not very closely related to other research topics. Cluster 2 was found in the second quadrant which was closer to the x axis and described fibroadenoma after living donor liver transplantation. The research on this topic was shown to be relatively mature. Density and centrality in the third quadrant are both low, and clusters in the third quadrant have a loose internal structure and are not closely related to other studies. They belong to the fringe research areas where their research areas have not received much attention. The research is not yet mature and needs further development. In the fourth quadrant, the density was relatively low and the

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centrality was high. Research in this quadrant had a certain potential for development, but because of its loose connections, the structure was unstable and easily decomposed, and no cluster was found in this quadrant.

Limitations

There are some limitations to our research. The input data of the bibliometric analysis software mentioned in the article mainly comes from PubMed. This database is more advanced in terms of journal source, country, author, and departments information. Therefore, we only analyzed the publication data in the PubMed database. We did not use multiple search engines (e.g., WoSSC, Scopus, Ovid, Google Scholar). Most publications in PubMed are written in English, which may be linguistically biased. We will consider multiple search engines for data analysis in future research.

Conclusions

For pediatric liver transplantation, we summarized 5 clusters and 7 hot topics. The current state of research in this field is polarized. Critical elements in pediatric allograft selection, surgical treatment for childhood hepatoblastoma, and food allergies developing after solid organ transplant are at the absolute core with the most mature research, and fibroadenoma after living donor liver transplantation is limited. Post-transplant lymphoproliferative disorder in pediatric patients and outcomes of multivisceral transplantation are very promising. Citation frequency analysis is also an important method for bibliometric research, and citation analysis of pediatric liver transplantation articles should be done in the future.

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