Heart Transplantation: A Bibliometric Review From 1990-2021

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Abstract: As the rapidly aging population and the rising incidence of end-stage heart failure, extensive research has been conducted on heart transplantation (HTx). Bibliometrics harbors the function for describing the relationships of knowledge structures in different research fields and predicting the growth trend. The publications were searched and filtered based on the Web of Science core database. The target literature was visualized and analyzed by CiteSpace or VOSviewer. In total, 19,998 published papers were obtained. There is a wave-like growth in HTx development. Most advanced research results are concentrated in a few developed countries, while the interactions with developing countries are still in infancy. The United States occupies a strong dominant position among active countries on HTx. Early research hotpots mostly focused on primary disease, survival risk factors, and complications. In recent years, the research frontiers have shifted steadily to clinical evaluation of immunosuppressants and diagnosis of acute rejection, cardiac re-injury with coronavirus disease 2019, innovations in ventricular assist devices, and donation allocation strategies. The

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research directions of HTx are gradually shifting from observational studies to intervention research. (Curr Probl Cardiol 2022;47:101176.)

Introduction

Globally, the overall incidence rate of heart failure (HF) continues to rise as a result of aging populations and the epidemic of cardiovascular diseases (CVD), presenting a severe threat to global public health worldwide.[1] Approximately 2% of adults worldwide suffer from chronic HF, and it is estimated that the prevalence of HF will increase by 25% in the next 20 years[2]. As HF is a progressive disease, approximately 10% of chronic HF patients who receive optimum treatment will still develop end-stage HF each year, and 50% of them will die within 5 years. Heart transplantation (HTx) is considered the last choice and gold standard treatment for end-stage HF when other alternative treatments have failed. Currently, The number of people who receive HTx each year has approached 5000, according to The Registry Of International Society for Heart and Lung Transplantation.[3,4] More than 80% of patients survive at least one year after HTx, while 57% survive for a decade.[5] Although the first human HTx operation occurred in 1967, it wasn't until the 1980s that HTx became the most effective treatment option for patients with end-stage HF due to the widespread use of cyclosporine.[6] However, the early application of HTx was severely limited by donor shortage, strict contraindications and complications. In recent years, HTx has enjoyed a resurgence with the improvement of organ allocation strategies and the progress of immunosuppressant.[7,8]

Generally, bibliometrics is considered as an advanced method to understand developmental stages in various emerging disciplines.[9] Literature visualization networks could potentially summarize and analyze the development process and the knowledge structure from the dimensions of time and space.[10] The development of HTx enjoys a history of nearly 60 years. Many countries have gained remarkable achievements in their in-depth and detailed investigation, but there is no bibliometric visual analysis on HTx. In this review, the knowledge maps of HTx were performed respectively by different bibliometrics software, to comprehensively demonstrate the collaboration network in representative countries and institutions, as well as provide a convenient and flexible way to identify and track emerging trends.[11]

Data Source and Method

Data Source

The core collection of Web of Science is applied as the data source. The search strategy used was as follows: (TS = [“heart graft*” OR “cardiac graft*” OR “heart transplantation*” OR “cardiac transplantation*”]) AND (Language = [English]) AND (document type = [“article” OR “review”]), the retrieval time was limited from January 1, 1990, to December 31, 2021. The following exclusion criteria screened the obtained literature: articles not officially published, meeting summary and meeting minutes, early online publication, repeated articles unrelated to the topic, book chapter; incomplete articles. Finally, A total of 19,998 publications were identified, including 17,647 articles and 2351 reviews. Fig 1 shows the steps involved in screening and analyzing data.

Method

CiteSpace, a visualization software runs under the Java language environment, focuses on finding critical points and turning points of emerging disciplines.[12] We exported the obtained literature in plain text format, including the titles, authors, abstracts, keywords, cited references, etc. The exported data were named “download_.txt,” which can be discerned by CiteSpace.[13] The parameters were selected as follows: Timespan: 1990-2021, Time slice: 2 years, Selection criteria: Top N per slice = 50 and the rest of the options were set to the default. VOSviewer takes a more concise view of international collaboration strength than CiteSpace, presenting nodes and links with greater clarity. Accordingly, we used VOSviewer1.6.17 to estimate the contributions and intensity of cooperation from countries and organizations. Moreover, the bibliometric mapping software Scimago Graphica was applied for country partnership analysis and institutional cluster analysis.

In co-occurrence networks accomplished by Citespace, the node size represents the frequency of occurrence, and the density of lines between nodes indicates the proximity of cooperation. The purple rings around the circles reflect the nodes with higher betweenness centrality (>0.1), which is a convincing sign associated with the transformative academic contribution.[11] Generally, nodes with the thicker purple circle are considered to have the potential to be the “Turning Point” or “Junction Station” connecting different clusters.[14] Clustering is a statistical method to classify

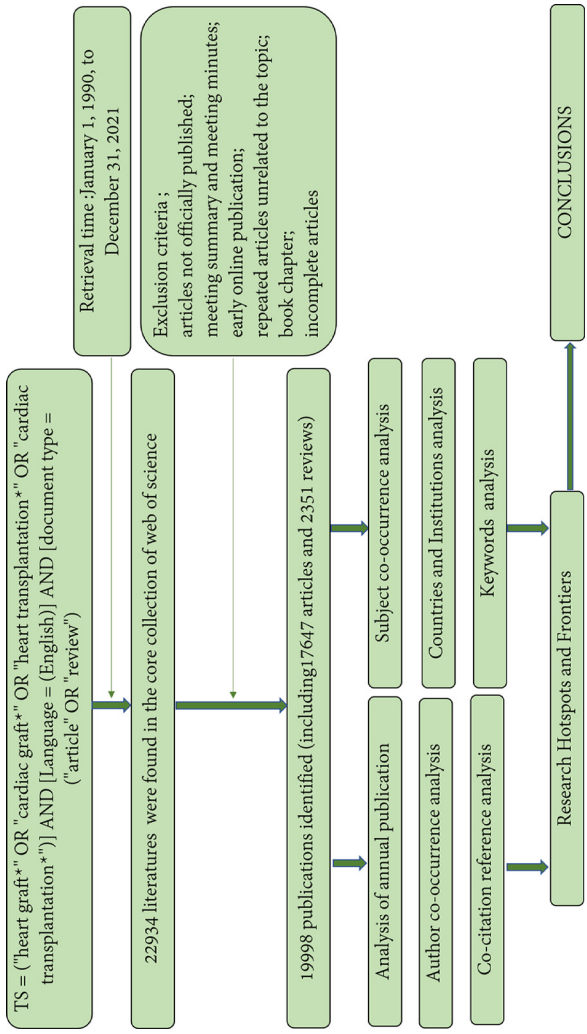

FIG 1. Flowchart of literature selection and scientific econometric analysis.

data according to similarity, which aims to find the distribution of main research contents.[15] The size of cluster is inversely proportional to the number, for example, cluster #0 is the largest cluster. If 2 articles appear in the bibliography of the third cited article at the same time, they form the co-citation relationship. Co-occurrence and cluster analysis of the co-citation literature were performed respectively to explore the common themes of analogous literature and discover the landmark literature. Furthermore, We plotted the co-cited reference timeline to display each cluster advance period and research progress in parallel. Finally, keywords clustering was accomplished to identify high-frequency keywords and significant clusters about HTx. The detailed procedure of literature screening and data analysis is shown in Fig 1.

Results and Discussions

Analysis of Annual Publication

The quantity and growth rate of annual publications represent the subject's progress pace and developmental potential to some extent. Fig 2 visually showed the yearly volume and trend of literature with histogram and curve, the bars corresponding to different years expressed a wave-like rise. The fold line indicating the growth rate is mainly located above the horizontal line, and the growth rate exceeds 10% in some years. The first peak occurred in 1996, representing the research on HTx set off an upsurge at the end of the last century. From 1997 to 2015, the number of documents increased slowly in waves and reached the second peak in 2015. Although the number of records issued decreased slightly after 2015, there was an explosion after 2017 and reached the third peak in 2020, indicating that the discussion on HTx in the recent 5 years has once again attracted more interest and stepped into a period of rapid development. The increase may be related to the expansion of the population with end-stage HF, the prevalence of coronavirus disease 2019 (COVID-19) and the widespread availability of HTx.

Subject Co-occurrence Analysis

The progress of emergence discipline has to blend and cooperate with other fields. We built a subject cooperation-related network (Fig 3) of HTx visually exhibiting the relationships between different disciplines. Table 1 listed the top 10 domains with the highest frequency. The cardiovascular system is undoubtedly the most crucial discipline in regards to

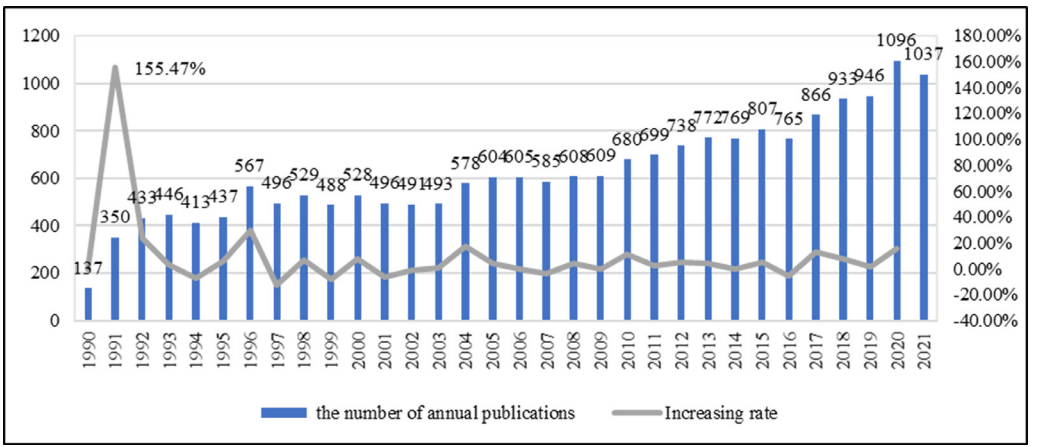

FIG 2. The number of annual publications related to HTx from 1990 to 2021.

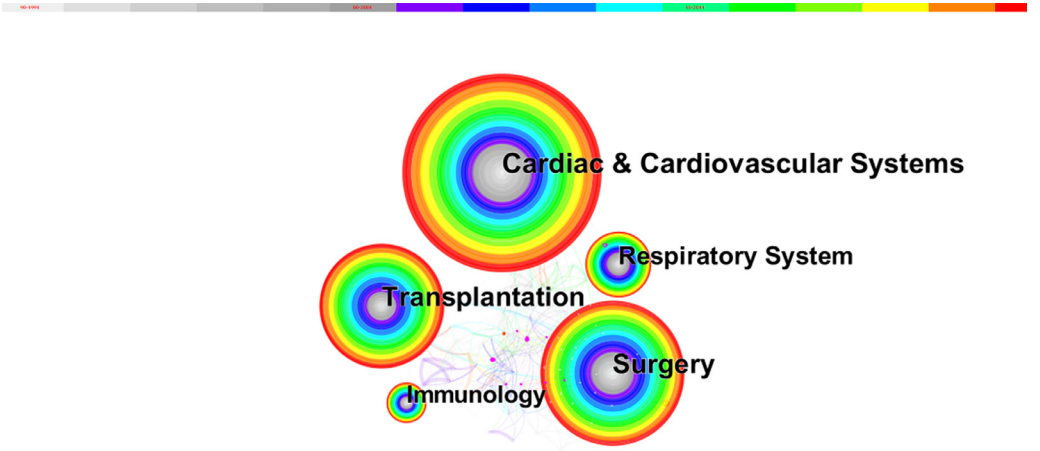

FIG 3. Co-occurrence of topic categories of articles on HTx.

TABLE 1. Top 10 subject categories of publications about HTx

Rank	Categories	Count	Centrality
1	Cardiac and cardiovascular systems	9483	0.04
2	Surgery	6900	0.01
3	Transplantation	6118	0.03
4	Respiratory system	3655	0
5	Immunology	2339	0.01
6	Medicine, general, and internal	976	0.04
7	Peripheral vascular disease	965	0.11
8	Pediatrics	831	0.12
9	Engineering, biomedical	623	0.08
10	Medicine, research, and experimental	589	0.21

heart transplantation, followed by surgery, respiratory system, and immunology. The collaboration of these disciplines has laid a solid foundation for the healthy and rapid development of HTX. In addition, engineering also played a significant role in the growth of HTx, which may be related to the extensive applications of ventricular assist devices (VAD).[16] As can be seen in Table 1, among the top 10 topic categories, Peripheral vascular disease, Medicine Research and Experimental, and Pediatrics had good median values (betweenness centrality >0.1), indicating that they serve as bridges to connect other disciplines. The co-occurrence results demonstrated HTx a typical interdisciplinary discipline closely associated with multiple fields. The top 10 cited journals were listed in Table 2. Nine of them were published in the US, with the most-cited journals was Circulation with 11,360 articles and the strongest betweenness centrality, followed by *Journal Of Heart And Lung Transplantation* and *New England Journal of Medicine*.

TABLE 2. Top 10 journals of publications about HTx

Rank	Cited journals	Frequency	Centrality	Country
1	*Circulation*	11,360	0.61	United States
2	*J Heart Lung Transpl*	11,278	0.29	United States
3	*New Engl J Med*	8349	0.15	United States
4	*J Am Coll Cardiol*	8044	0.09	United States
5	*Transplantation*	7807	0.34	United States
6	*Ann Thorac Surg*	6049	0.11	United States
7	*J Thorac Cardiov Sur*	5897	0.03	United States
8	*Am J Cardiol*	5733	0.16	United States
9	*Lancet*	4412	0.03	England
10	*Transplant P*	4203	0.05	United States

Author Co-occurrence Analysis

Generally, author co-occurrence analysis is used to identify the most influential authors and assess the cooperation ability between different teams. The author's collaboration network map was displayed in Fig 4 with 640 nodes and 952 lines. The top 10 productive authors' detailed information was shown in Table 3, including the number of publications and the link strength.

The author who published the most papers was Frazier OH, the director of cardiovascular surgery research at the Texas Heart Institute. He focused on the improvement and multicenter clinical evaluation of cardiac mechanical ventricular electrical assistance systems.[17,18] According to his research results, continuous-flow left ventricular assist devices (LVAD) could provide effective hemodynamic support for patients with refractory HF for 6-18 months,[19,20] which significantly has risen much attention and promoted the clinical application of VAD. Yoshifumi Naka, a representative of another academic team, proposed that continuous-flow -LVAD could improve patients' quality of life and survival function waiting for HTx.[19] Still, the utilization of these devices increases the risk of bleeding at the same time.[21] Based on his research, studies on complications of VAD have gradually received more attention. The rejection of allogeneic organs by autoimmune system is a double-edged sword for transplant patients. Professor Kirklin carried out earlier research on the risk factors of rejection after heart transplantation, including gender, age, and infection,[22] and took the lead in paying attention to the field of pediatric heart transplantation caused by congenital heart disease.[23] As another expert in pediatric heart transplantation, Professor Hetzer has demonstrated that pediatric ventricular assist devices could be used as alternatives to HTx.[23]

The academic teams with close internal links were concentrated in developed countries, but the communication between teams in different regions and countries required to be strengthened. A specialized organization is expected to be established to address this issue with a wide range of learning and communication activities.

Countries and Institutions Co-occurrence Analysis

To evaluate the development level of HTx in different countries and figure out the potential cooperative relationships, we constructed the co-occurrence networks of country and institution, respectively. Figs 5A and B depicted national interactions involved with HTx, whereas various clusters of the country's cooperation on HT were displayed in Figs 5C

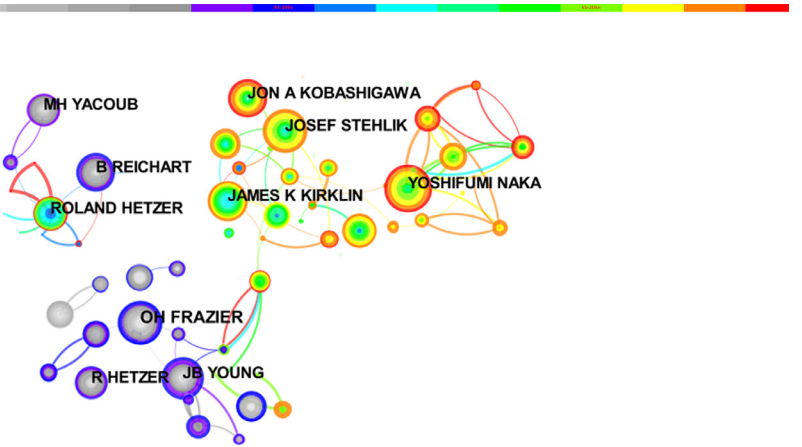

FIG 4. Co-occurrence of authors on HTx. The size of circles represents the number of articles published; the links describe the degree of communication and interactions between authors.

TABLE 3. Top 10 productive authors of publications about HTx

Rank	Author	Count	Centrality	Year
1	Oh Frazier	92	0.01	1990
2	Yoshifumi Naka	86	0.01	2006
3	James K Kirklin	83	0.03	2007
4	Jb Young	78	0.06	2006
5	R Hetzer	74	0.01	2006
6	Jon A Kobashigawa	72	0	1991
7	Roland Hetzer	71	0.03	1991
8	Mh Yacoub	71	0	1992
9	Josef Stehlik	70	0.07	2008
10	B Reichart	69	0.02	1991

and D. As displayed in Table 4, each of the top 5 countries had published more than 1000 articles and the betweenness centrality was more than 0.1, indicating that developed countries, such as the United States, Germany, Britain, Italy, and Canada were in the world-leading position on HTx and made contributions that cannot be ignored. It is worth noting that the number of articles issued by the US exceeded the sum of the number of papers published by the remaining 4 countries and maintained a high centrality since 1990, which fully proved its outstanding achievements on HTx. China is the only developing country among the top 10 countries and has gradually participated in HTx research in recent years and achieved rapid progress. Furthermore, cluster analysis reveals that the top 30 countries form 5 modules of closer cooperation, with the US, Germany, and Italy collaborating the most frequently.

It is undeniable that developed countries firstly paid attention to and implemented HTx, several academic groups active in HTx were subsequently formed in these countries after decades of development. A total of 634 institutions were included in the institution co-occurrence analysis map (Fig 6). All 9 of the top 10 institutions are located in the US, which could explain the US such a large number of documents and strong centrality (Table 5). The fact that Stanford University contributed the most documents and the total link strength is due to its academic influence, highly cooperative scientific research model, and sufficient scientific research foundation. According to the results of the institutional cooperation network and cluster result, there is extensive cooperative research among influential institutions, but it is predominantly centered around the developed countries represented by the US. Comparatively, research and cooperation on HTx are relatively weak in developing countries.

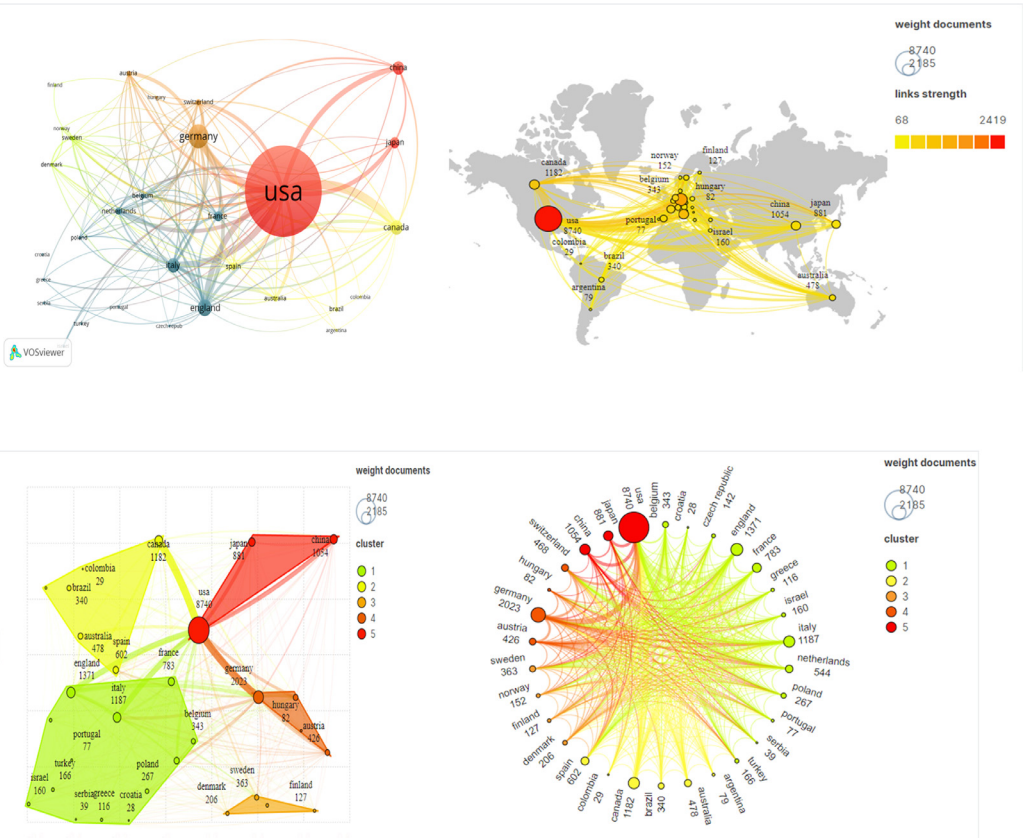

FIG 5. (A) An interactive map of countries involved in HTx research made by VOSViewer. (B) A world map showing the number of publications and the strength of collaborations among countries. (C) Clustering map of different national collaborations. (D) A circle diagram that evaluates international collaboration between clusters.

TABLE 4. Top 10 countries of publications about HTx by count

Rank	Country	Documents	Centrality	Total link strength
1	USA	8740	1.14	2419
2	Germany	2023	0.21	1416
3	England	1371	0.34	1122
4	Italy	1187	0.25	1031
5	Cananda	1182	0.19	872
6	China	1054	0.01	438
7	Japan	881	0.05	349
8	France	783	0.21	600
9	Spain	602	0.22	524
10	Netherlands	544	0.06	646

TABLE 5. Top 10 institutions of publications about HTx by count

Rank	Organization	Documents	Total link strength
1	Stanford Univ	512	1045
2	Univ Pittsburgh	484	887
3	Harvard Univ	472	803
4	Columbia Univ	442	910
5	Mayo Clin	355	512
6	Univ Calif Los Angeles	352	633
7	Univ Toronto	289	679
8	Univ Penn	280	675
9	Washington Univ	251	770
10	Duke Univ	240	680

Co-citation Reference Analysis

Articles with high citations could reflect the critical points, and the number of citations represents the quality of research to some extent.[24] Each cited reference was represented as nodes of different sizes in Fig 7, and the timeline view was presented in Fig 8. Table 6 summarized the primary information of the top 5 most commonly cited references, and the top 5 literature according to betweenness centrality were presented in Table 7.

It should be indicated that the type of top 5 articles were all academic guidelines[25] or annual reports[3] of transplantation centers, illustrating the fundamental supporting role of the International Society for Heart and Lung Transplantation and the European Society of Cardiology in the field of HTx. The most cited article was the 2016 guidelines for diagnosis and treatment of HF formulated by the European Society of Cardiology.[26] This guideline suggested that HTx could significantly improve the survival rate, exercise ability, and quality of life compared with traditional

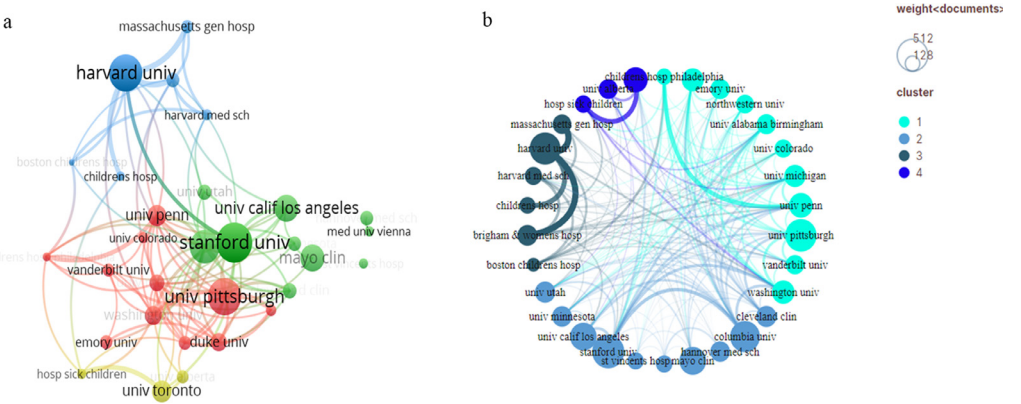

FIG 6. (A) An interactive map depicting institutional collaborations on HTx. (B) A circle map for assessing international collaboration between clusters. Circles represent institutions nodes; Links represent communication and interactions between institutions.

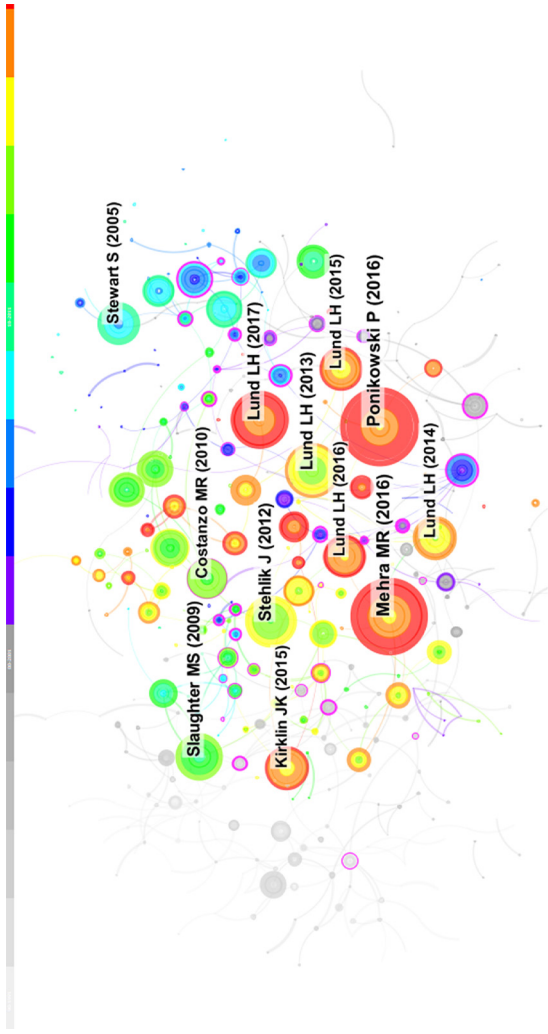

FIG 7. Co-occurrence of co-citation references on HTx.

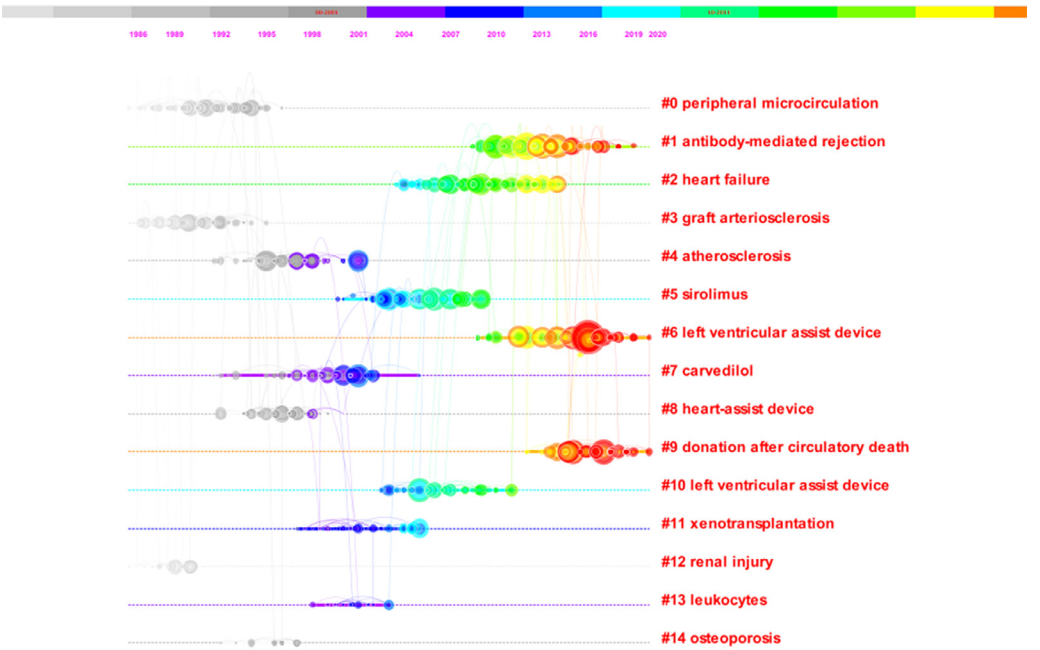

FIG 8. Timeline view of references. The horizontal line represents the cluster type. Circular nodes represent cited documents. Links between nodes define co-citation relationships. Cluster IDs are arranged in sequence on the right side of the figure.

TABLE 6. Top 5 co-citation references of publications about HTx by frequency

Rank	Co-cited reference	Centrality	Source	Year	Frequency	Average per year
1	The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-y update	0.04	*J Heart Lung Transplant*	2016	264	52.80
2	2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC	0.07	*Eur Heart J*	2016	263	52.60
3	The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult heart transplantation report-2017; focus theme: allograft ischemic time	0.03	*J Heart Lung Transplant*	2017	194	48.50
4	The Registry of the International Society for Heart and Lung Transplantation: thirtieth official adult heart transplant report—2013; focus theme: age	0.09	*J Heart Lung Transplant*	2013	188	23.50
5	The Registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report—2012	0.1	*J Heart Lung Transplant*	2012	182	20.22

treatment. The other guideline revised by the International Society for Heart Lung Transplantation also ranked first. It further modified the indications and contraindications of HTx, as well as called for the subjective initiative of doctors concerned when selecting the appropriate recipients.[27] The above 2 guidelines were more abundant and systematic in elaborating HTx utilization status than the previous ones and provided

TABLE 7. Top 5 co-citation references of publications about HTx by centrality

Rank	Co-cited reference	Centrality	Source	Year	Frequency
1	Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant	0.4	*Circulation*	1997	34
2	Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling	0.38	*Am J Transplant*	2006	48
3	Effect of carvedilol on survival in severe chronic heart failure	0.38	*N Engl J Med*	2001	40
4	Effect of receiving a heart transplant: analysis of a national cohort entered onto a waiting list, stratified by heart failure severity. Comparative Outcome and Clinical Profiles in Transplantation (COCKPIT) Study Group	0.38	*BMJ*	2000	17
5	Long-term use of a left ventricular assist device for end-stage heart failure	0.37	*N Engl J Med*	2001	108

more comprehensive guidance for further application of HTx. The International Heart and Lung Transplantation Registry made a statistical analysis about HTx cases submitted by centers worldwide every year and contributed the influential detailed analysis on a specific theme in the annual report since 2013. Among the controversial issues, the reports focusing on ischemia time of allogeneic[3] and age[28] had the most citations, ranked third and fourth, respectively. Age and allograft ischemia time were independent risk factors for complications and mortality. The risk of death increases dramatically with increasing ischemic time in allografts. Despite the unfavorable interaction of age and survival time, there are significant differences in complications and causes of death among age groups.[3,28]

Betweenness centrality quantifies the number of times a node acts as a bridge on the shortest path between other nodes. Among the networks of references cited, the article with the highest betweenness centrality was "Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transfer evaluation," published in Circulation in 1997. This research put sight to noninvasive

risk stratification of patients with end-stage congestive HF, which offered essential thoughts for more effective coordination between scarce donor organs and a large pool of candidates.[29] The article ranked second mainly focused on the critical role of gene expression detection in evaluating clinical events and immune rejection.[30] The indispensable role of VAD in improving the survival rate and quality of life of patients with end-stage HF has also been confirmed in the third article, which established an evidence-based medical foundation for VAD as the alternative therapy for HTx.[31]

The timeline view is a visualization method of time slicing technology based on clustering. It is widely recognized that it can describe the changes of heated topics while summarizing the distribution of research topics. Fig 8 visually displayed the transformations of hotspots of co-cited literature clusters over time. In the early stage, the leading research concentrated on the risk factors of HTx, including peripheral microcirculation(cluster#0), risk factors (cluster#3, cluster#4), post-transplant complications (cluster#12, cluster#14, cluster#7). Since the 21st century, researchers have gradually turned their attention to immune rejection and immunosuppressants (cluster#1, cluster#13, cluster#5), ventricular assist device (cluster#6, cluster#8), and donor allocation (cluster #9).

Keywords

It could be argued that keywords capture the direction of the publication's research and effectively distill its essential content. In contrast, when the number and type of keywords were too complex, the research topics were so ambiguous that it was difficult to determine the current research hotspots and priorities. It is possible to solve this problem with keyword clustering, which could extract representative phrases from keyword groups with similar meanings as specific cluster labels. Keywords ranked among the 20 top keywords mainly include HTx, HF, survival, rejection, mortality, outcome, international society, VAD, risk factor, coronary artery disease, children, cardiomyopathy, immunosuppression, diagnosis, cyclosporine. Keyword clustering microscopically revealed and refined the topic distributions of HTx. The keyword clustering result (Fig 10, Table 9) and co-occurrence result (Fig 9, Table 8) were summarized as follows: ventricular assist device (clustering#0), immune rejection and immunosuppressive therapy (clustering #1, clustering #9), primary disease (cluster#3, cluster#4, cluster#10), and complication and survival (cluster#2, cluster#7).

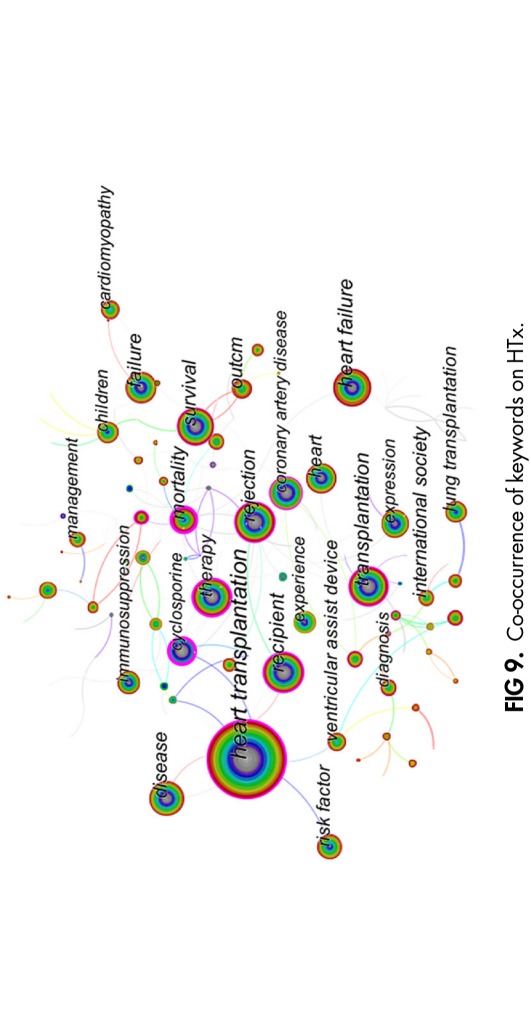

FIG 9. Co-occurrence of keywords on HTx.

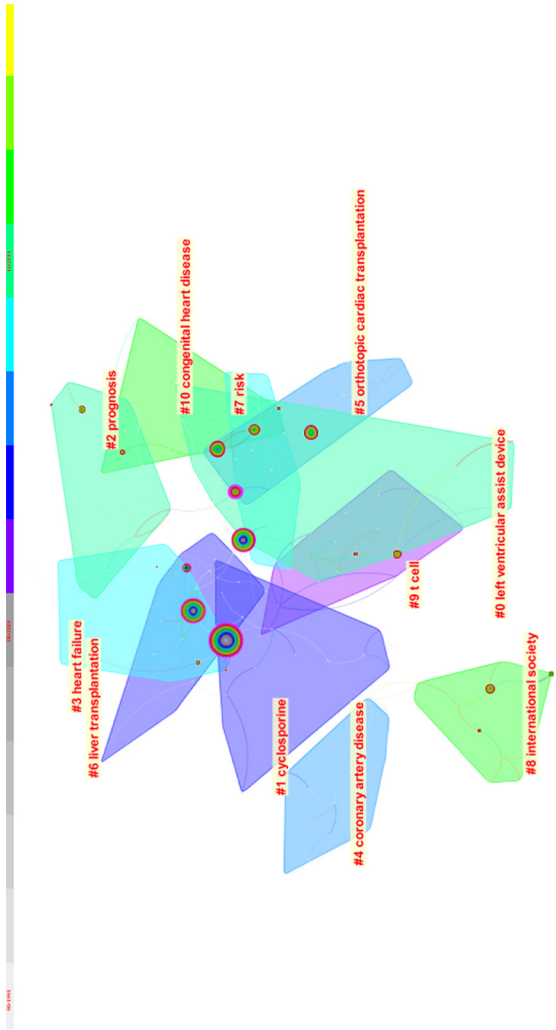

FIG 10. The clusters of keywords based on the log-likelihood ratio (LLR) algorithm.

TABLE 8. Top 20 keywords of publications about HTx by frequency

Rank	Keyword	Frequency	Centrality	Rank	Keyword	Frequence	Centrality
1	Heart transplantation	8073	0.15	11	Lung transplantation	970	0.03
2	Heart failure	2072	0.12	12	Ventricular assist device	902	0.05
3	Recipient	1980	0.2	13	Risk factor	863	0.05
4	Transplantation	1976	0.3	14	Coronary artery disease	829	0.14
5	Survival	1789	0.14	15	Children	827	0.12
6	Rejection	1446	0.13	16	Cardiomyopathy	794	0.01
7	Mortality	1254	0.08	17	Expression	758	0.11
8	Outcome	1211	0.05	18	Immunosuppression	683	0.06
9	International society	1200	0.07	19	Diagnosis	662	0.07
10	Therapy	972	0.05	20	Cyclosporine	661	0.1

TABLE 9. Cluster size and representative keywords

Cluster ID	Silhouette	Top terms (LLR)
0	1	Left ventricular assist device; cardiogenic shock
1	0.946	Cyclosporine; acute rejection; COVID-19
2	0.968	Prognosis; echocardiography; myocarditis
3	0.984	Heart failure; rejection; allograft vasculopathy
4	1	Coronary artery disease; atherosclerosis; hyperlipidemia
5	0.956	Orthotopic cardiac transplantation; congestive heart failure
6	0.967	Liver transplantation; kidney transplantation
7	0.927	Risk; mortality; rejection
8	1	International society; registry pulmonary hypertension
9	1	T cell; activation
10	1	Congenital heart disease; children; survival

Discussion

Based on the co-cited literature timeline view and keyword clusters, we outlined the research hotspots and frontiers about HTx from the following aspects: From 1986 to the end of the 20th century, we observed risk factors, complications, survival rates, and primary diseases of HTx attracted the interest of researchers. With the widespread of immunosuppressants and the expansion of the transplantation population, research interest and frontiers have gradually shifted to the optimal therapy of immunosuppressants, cardiac re-injury after COVID-19, the creative inventions of VAD, and exploration of donor organ allocation strategies.

Primary Disease

The type of primary disease is closely related to the survival and prognosis of HTx. Among all transplant recipients, non-ischemic dilated cardiomyopathy was the most common essential diagnosis, followed by ischemic heart disease, congenital heart disease, heart valve disease, etc.[32] The most common cause of HTx in children is congenital heart disease, which is particularly difficult to be addressed by drugs treatments or other surgical interventions. In the last three decades, advances in surgical techniques and better detection have made it possible for many children to survive, but some still suffer end-stage heart failure. It is estimated that 46% of children with HF die or receive transplantation within 5 years after diagnosis.[33]

Complication and Survival

The survival rate after HTx is higher than any other treatment for advanced HF. At present, the 1-year survival rate is approximately 86%, and the 5-year survival rate can reach 69%.[34] The leading causes for death after HTx changed over time. Graft failure and multiple organ failure were the most common causes of death in the first 30 days after transplantation, accounting for 40.5% and 17.6%, respectively.[5] In the first three years, vascular graft disease, multiple organ failure, and infection continued to play the dominant role, while 3-5 years later, vascular lesions, malignant tumors, and renal failure have gradually become the chief causes of death. In the longer-term follow-up (>5 years), malignancy was the principal cause of death.[35] Since the 21st century, the improvement of the short-term survival rate of HTx patients has stabilized, but the long-term survival rate has not improved significantly.[36]

Immune Rejection and Immunosuppressant

The Shumway team of Stanford University performed the first adult HTx in the United States on January 6, 1968, but many of the first recipients soon died of organ rejection or post-transplant infection.[37] Since 1976, the Stanford Research team began to use azathioprine plus corticosteroids to improve the prognosis of transplantation, but it was not until the clinical application of cyclosporine in the 1980s that the prognosis and survival rate after HTx was significantly improved.[38] Immunosuppressive therapy mainly includes immune induction, immune maintenance, and anti-rejection therapy.[39]

The immune response of the donor's heart begins with the recognition of alloantigen by immature T cells (keyword cluster 9). It leads to the activation of calcineurin and dephosphorylation nuclear factor of activated T cells, which start the transcription of interleukin-2 (IL-2). The binding of IL-2 and its receptors activates mammalian rapamycin target to provoke T cell proliferation and differentiation. The purpose of immune induction therapy is to provide intensive immunosuppression to reduce the risk of acute rejection episodes when the risk of organ rejection is highest. IL-2 receptor antagonists basiliximab are typically used to induce immune tolerance and to reduce acute rejection and early postoperative complications after HTx,[40] but not every recipient benefits from immune induction therapy.[41] There is still a need to confirm the effectiveness of immunization induction protocols in different races, ages, and medical conditions.[39]

For HTx recipients, triple therapy remains the most commonly used immunosuppression regimen. Cyclosporine (keyword cluster 2) was the first commercialized calcineurin inhibitor (CNI).[42] The combination of cyclosporine, azathioprine, and steroids could significantly improve the survival rates of recipients and reduced the infection by organ rejection. It can be stated that cyclosporin brought about a revolutionary change in HTx. But at the same time, it also caused severe adverse reactions, such as hypertension, diabetes, and chronic kidney injury.[37] Compared with cyclosporine, tacrolimus has fewer negative effects for its stable pharmacokinetics and pharmacodynamics.[43] The discovery of mycophenolate mofetil (MMF) was another critical advance in immunotherapy. MMF could selectively inhibit the proliferation of T and B cells compared with azathioprine.[37,44] Because of its significant specificity, MMF quickly replaced azathioprine in most clinical research centers. Another breakthrough in maintenance immunosuppression came with the emergence of mammalian rapamycin target inhibitors, which block the proliferation of immune cells by inhibiting the cell cycle. Compared with calcineurin inhibitor, Sirolimus (co-citation cluster 5) effectively reduced acute rejection and adverse events to improve patients' late survival.[45,46]

Rejection is one of the leading causes of death in heart transplant recipients, despite the fact that 85% of rejections can be reversed with intravenous glucocorticoids.[39] An endomyocardial biopsy is the gold standard for diagnosing acute rejection, but it is limited by uneven medical conditions and biopsy time. In order to identify and manage early acute rejection early, noninvasive and rapid detection of early rejection could be the next critical step.

Most patients after HTx have to receive a synergistic combination therapy of multiple immunosuppressants. Ideally, patients should take a minimum number and dose of the drug combination, dynamically adjust them to achieve maximum efficacy, and avoid severe adverse reactions.[47] Despite many basic and clinical trials, a convenient effective immunosuppressive regimen has not been found. Accordingly, we predict how to achieve dynamic balance quickly between immunosuppressive medication complications, rejection risk, and immunosuppressive therapy may continue to be a research hotspot.

The crucial topic that must be mentioned is that COVID-19 has made a difference to HTx patients. It was reported that some patients require HTx because of adverse events such as explosive myocarditis and cytokine storm after infection with COVID-19.[48,49] Additionally, researchers have found that the serum conversion rate of COVID-19 vaccination in HTx patients is lower due to immunosuppression.[50] Obviously, with the pandemic of COVID-19, severe cardiovascular damages induced by the COVID-19 on HTx patients will continue to capture the world's eyes for quite some time.

Ventricular Assist Device

There is no doubt that HTx is the definitive treatment of end-stage HF. However, the number of patients with end-stage HF far exceeded donor's hearts and many of them have contraindications to HTx. In this case, VAD began to emerge as transitional bridges for HTx. Since the 21st century, VAD therapy has progressively advanced from a method limited to bridging to a purposeful treatment.[51] According to the most recent HF guidelines published by the *American College of Cardiology and American Heart Association* in 2013, LVAD was suitable for patients with stage D HF with reduced ejection fraction, estimated to include 100,000-250,000 patients.[52,53] The early auxiliary equipment mainly relied on the pneumatic drive and pulsating flow, which led to a significant-high incidence of equipment failure and low survival rate.[51] The subsequent emergence of HF continuous-flow ventricular assist device promoted the solutions to these problems. In the past ten years, HeartMate II, HeartMate III (HM3), and Heart Ware HVAD were widely used in the US and Europe. HM3 can be implanted in the pericardium because of its smaller size and flatter surface, freeing patients from depending on a pump pocket and reducing the infection risk.[54] In the recently randomized controlled trials trial in multicenter, HM3 showed advantages in stroke and comprehensive survival compared with HeartMate II.[55] Although significant progress about VAD has been achieved, there are still serious adverse

events, including stroke, infection, and bleeding. At present, the 1-year and 2-year survival rates of patients after VAD implantation are 81% and 70%, respectively.[56] The 5-year survival rate of VAD patients is 30%, which is lower than HTx.[57] Keyword clustering shows that medical management, artificial heart, radio supply and genetic engineering have the ability to become the development direction in the future.[56] Moreover, an alternative treatment option to HTx, extracorporeal membrane oxygenation, has also gained interest from researchers in the past few years. However, it is generally used for rescue treatment of refractory heart failure as a result of its high cost and complexity.[58] As a recent study that successfully transplanted transgenic porcine hearts in situ confirms, cardiac xenotransplantation may prove to be a viable alternative treatment for patients with heart failure who don't qualify for VADs or human heart transplants.[59]

Organ Allocation

Donor and recipient characteristics and interactions are important factors influencing the outcome after transplantation.[60] The annual number of listed candidates for HTx is increasing, whereas the number of available donors stagnates, resulting in an ever-widening supply-demand mismatch.[61] In 1984, a bill of the US Congress sponsored the establishment of The United Network for Organ Sharing, which aims to promote the fair sharing of organs in the US and ensure that organs reduce ischemia time as much as possible.[62] The bill was a profound step for organ transplantation from a chaotic distribution mode to a fair, reasonable, and efficient distribution scheme. HTx distribution is guided by the principle of allocating organs to those most in need. However, with the increase of patients waiting for HTx, the proportion of people listed as the highest priority of medical emergency dramatically expanded. By 2011, the proportion of such transplant patients had increased to 56.3%,[63] which made it challenging to implement the principle of giving priority to those who need it most. Singh et al.[64] combined the mortality before HTx waiting list and survival after HTx to calculate the net survival benefit of HTx patients in the US to guide the distribution model, which may be a promising step towards a new organ distribution system.

Limitations

Firstly, data completeness is insufficient. The database selection was limited to the core collection of Web of Science and ignored other databases, such as PubMed and Scopus because the literature exported from

other databases was not recognized by the bibliometric software. Secondly, the quality of the studies is highly variable, for example, some of the high-quality literature was not adequately analyzed due to late publication dates or insufficient citations.

Conclusions

In this review, the bibliometric software CiteSpace and VOSviewer were applied to visualize and analyze the articles related to HTx from 1990 to 2020, mainly related to the core authors, countries and institutions, subjects, critical articles and keywords. We observed that the development of HTx displayed a wave-like rise from 1990 to 2021, with the regional imbalance in different countries and institutions. A few developed countries mastered the advanced core technology of HTx and have established a systematic, complete and standardized HTx system. However, the interactions of significant countries remains frail. It is necessary to establish international organizations specializing in transnational and cross-team collaboration to achieve balanced and extensive growth globally. HTx is the epitome of the coordinated development of engineering and clinical medicine. Its further development depends on the progress of engineering and science technology. Consequently, more attention should be paid to cultivating compound talents with medical backgrounds in future medical education. The early HTx related research mainly focused on the primary diseases, survival risk factors, and complications. Presently, the hotspots have gradually turned to the clinical evaluation of immunosuppressants, cardiac re-injury after COVID-19, the advance of VAD, and donor allocation strategies. We predicted that the future research trends in immunology about HTx will focus more on evaluation of immune induction, balance scheme of immune maintenance and diagnosis of rejection. Future frontiers on VAD will likely focus on the optimization of device performance, the innovation of micro and minimally invasive VADs, and the collaboration between innovative engineering and medical management. This review complements traditional reviews and scientific articles in bibliometrics. We expect that our study could provide clinicians and trial investigators with objective quantitative visualization of the literature and stimulate their interest in HTx to benefit patients with end-stage HF.

Summary

The purpose of this review is to complement research on cardiac transplantation from a scientometric perspective and provide researchers with

overview of current research hotspots and the frontiers prediction of heart transplantation by visual analysis of literature.

Authors' Contributions

YHD and YHH designed the research methods, formulated research plans, and was responsible for statistical analysis. YHD and XPZ were accountable for literature and data processing. CLD and YHY are responsible for the production of pictures and tables. NMW, YZ, and GZY modify the first draft. YHH provided suggestions for the revision of the final draft. All authors contributed to the article and approved the submitted version.

Language Editing Statement

We are willing to accept the further language touch-ups and edits if required.

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