



Immune response in heart transplantation: a bibliometric analysis

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Background: Heart failure is the end stage of various heart diseases. For patients with poor or ineffective response drug treatment, heart transplantation is a reasonable and effective option. With the accumulation of heart transplantation cases, there are more and more studies on the immune response after heart transplantation. The purpose of the present study was to provide a bibliometric analysis of the current status of studies related to immune responses after heart transplantation.

Methods: We searched the Science Citation Index Expanded online database with the following search terms: “heart transplantation” and “immune response”. CiteSpace software was used to analyze the search results, including the annual trend in the number of publications, the annual trend in the number of citations, the distribution of the countries and institutions to which the authors belonged, the distribution of authors, the distribution of the journals that published the literature, and the use of keywords.

Results: A total of 1,393 related research papers were included. The top five countries with the greatest number of published papers were the USA, China, Germany, the UK, and Japan. The countries with active cooperation with other countries were the USA, the UK, Germany, China, and Canada. The top five research institutions with the greatest number of published papers were the University of Pittsburgh, Harvard University, Washington University, Stanford University, and Brigham & Women's Hospital. The research institutions with active cooperation with other institutions were the University of Pittsburgh, Stanford University, Harvard University, Brigham & Women's Hospital, and Harvard Medical School. The top five authors with the most published papers were David K. C. Cooper, Hidetaka Hara, Hayato Iwase, David Ayares, and Cassandra Long. Core journals were *Transplantation*, *Journal of Immunology*, and *Proceedings of The National Academy of Sciences of The United States of America*. Keyword analysis revealed that research hotspots changed over time.

Conclusions: Research on immune response after heart transplantation is concentrated in a few countries, and more clinical research is needed in the future.

Keywords: Immune response; heart transplantation; bibliometric analysis

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Introduction

Cardiovascular disease is one of the main diseases that endanger human health and life, and heart failure is the end stage of various cardiovascular diseases, especially

hypertension, coronary heart disease and valve heart disease (1). There were about 37.7 million heart failure patients worldwide in 2010 (2). Another study found that there were about 100–900 new cases of heart failure per 100,000 people each year (3). Despite significant

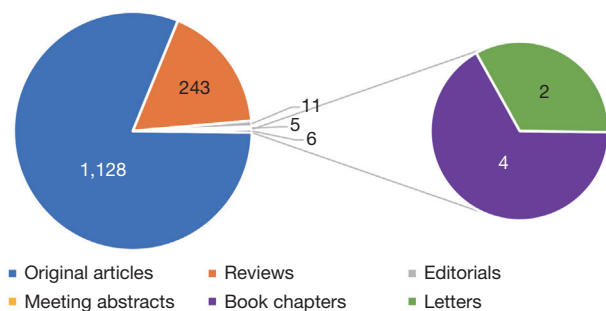


Figure 1 There were six types of literatures in the present study.

advances in drug therapy in recent decades that have greatly improved the outcomes of heart disease patients, a large number of patients still end up dying from heart failure (4). For patients with poor or ineffective response to drug treatment, which suggested that the heart failure is refractory, heart transplantation is a reasonable and effective option (5,6). From 2015 to 2018, a total of 1,583 heart transplants were conducted in 35 heart transplant centers in mainland China, and the trend is increasing annually (7). However, like other organ transplants, heart transplantation also causes immune response of the recipient's body to the donor heart, mainly manifested as postoperative rejection (8,9). Endocardial myocardial biopsy (EMB) is the gold standard for monitoring rejection after heart transplantation. However, the monitoring of the degree of immunosuppression after transplantation is significantly limited due to the invasive nature of EMB detection. In recent years, it has become increasingly known that acute antibody-mediated rejection (AMR) could be more harmful than acute cellular rejection (ACR), and the prognosis of AMR patients is worse than that of ACR patients (10). With the accumulation of heart transplantation cases, there are increasing studies on the immune response after heart transplantation. Bibliometrics is a statistical analysis of related papers on a specific topic, and the results can reflect the research status of a specific field, including the main countries, research institutions, researchers, and the main journals that publish related literature. The analysis of keywords reflects changes in the focus of relevant research (11). Science Citation Index Expanded (SCI-E) is currently the main database for bibliometric analysis (12). The purpose of the present study was to provide a bibliometric analysis of the current status of studies related to immune responses after heart transplantation.

Methods

Data source

The SCI-E online database was used as the data source.

Search strategy

The literature search time of the present study was from the earliest time of publication in the database to the latest time of literature publication, and the last search time was December 3, 2021. The search strategy adopted was "topic" search, and the search terms were "heart transplantation" and "immune response". Deduplication criteria were as follows: (I) online published literature records that duplicate the final officially published literature; (II) conference papers, abstracts, letters, and briefings that duplicate the officially published literature; and (III) revision and retraction. Repeatedly published literature were removed according to deduplication criteria.

Analysis

The search results were stored as raw data files in plain text, and CiteSpace software (Drexel University, USA) was used to analyze the raw data files. The contents of the analysis included the annual trend in the number of publications, the annual trend in the number of citations, the distribution of the countries and institutions to which the authors belong, the distribution of the authors, the distribution of the journals that published the literature, and the use of keywords.

Statistical analysis

CiteSpace software was used to analyze literature-related indicators, and the data were mainly expressed as number and percentage.

Results

General information

In the study of immune response after heart transplantation, a total of 1,492 related research literature records were retrieved, 99 duplicate literatures were removed according to the de-duplication standard, and the final literature count was 1,393 (Figure 1), with a total of 43,624 citations. The average number of citations of the literature was 31.32,

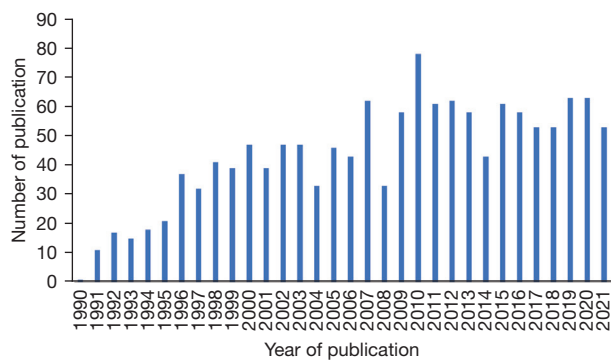


Figure 2 In the early years [1990–2000], the number of publications of these papers showed an increasing trend. After 2000, there was a fluctuating trend.

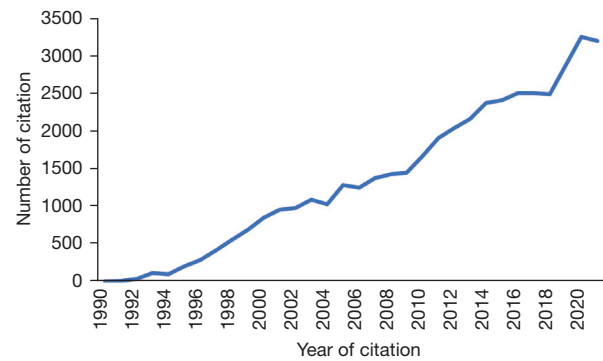


Figure 3 The number of citations increased annually.

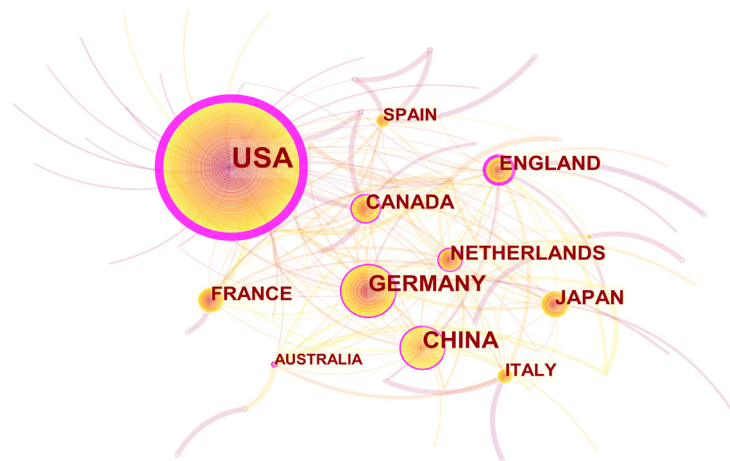


Figure 4 Country visualization map showed that USA had the most publications and collaborations with other countries.

and the h-index, which reflects the citation degree of the literature, was 94. Of the 1,393 literatures, there were 1,128 original papers, 243 reviews, 11 editorials, 5 meeting abstracts, 4 book chapters, and 2 letters. In the early years [1990–2000], the number of publications of these papers showed an increasing trend. After 2000, there was a fluctuating trend (Figure 2). However, due to the continuous accumulation of the number of papers published, the number of citations of the papers showed an increasing annual trend (Figure 3).

Countries

The visualization map of the country to which the author

belongs was generated by CiteSpace V software (Figure 4). There were 78 nodes in the map, and 198 connections between the nodes (Figure 4). Each node represents a country, and the larger the node, the greater the number of literatures that the country published. Each line represents the cooperation between the two countries in the same literature. Therefore, the more countries that cooperated, the denser the connections around their nodes. Data analysis showed that the top five countries with the largest number of published articles were the USA, China, Germany, the UK, and Japan (Table 1). The top five countries with the highest centrality scores reflecting cooperation were the USA, the UK, Germany, China, and Canada (Table 2).

Table 1 Top 10 countries by number of publications

Rank	Country	Publications (n)
1	USA	653
2	China	172
3	Germany	158
4	England	90
5	Japan	86
6	Canada	83
7	The Netherlands	77
8	France	72
9	Italy	48
10	Spain	42

Table 2 Top 10 countries for centrality

Rank	Country	Centrality
1	USA	0.86
2	England	0.27
3	Germany	0.15
4	China	0.13
5	Canada	0.13
6	Australia	0.11
7	The Netherlands	0.10
8	Spain	0.09
9	Italy	0.07
10	Japan	0.06

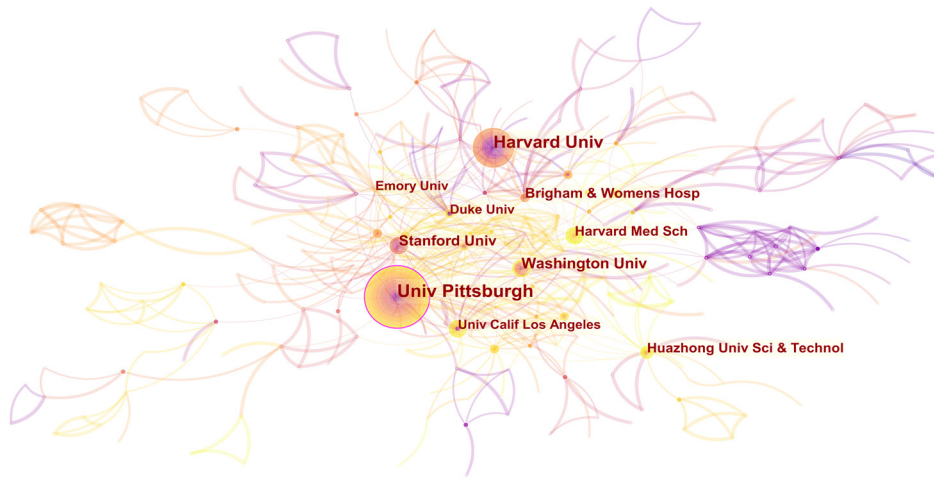


Figure 5 Institutional visualization map showed that University of Pittsburgh had the most publications and collaborations with other institutions.

Institutions

The visualization graph of the institutions to which the authors belong was generated by CiteSpace V software, and indicated that there were 657 nodes in the graph and 897 connections between the nodes (Figure 5). Each node represents a research institution, and the larger the node, the greater the number of literatures published by the institution. Each line represents the collaboration between the two research institutions in this paper. Therefore, the more collaborative research institutions, the denser the connections around their nodes. Data analysis shows that

the top five research institutions with the largest number of published papers were the University of Pittsburgh, Harvard University, Washington University, Stanford University, and Brigham & Women's Hospital (Table 3). The top five research institutions with the highest centrality scores reflecting collaboration were the University of Pittsburgh, Stanford University, Harvard University, Brigham & Women's Hospital, and Harvard Medical School (Table 4).

Authors

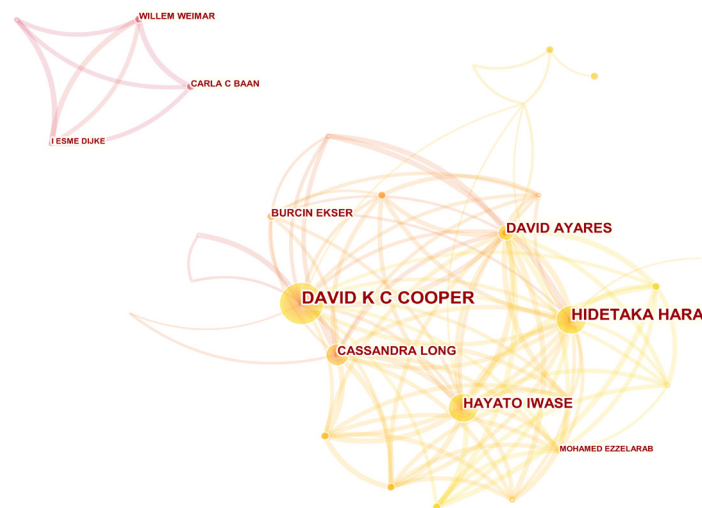
The visualization map of the authors of the literature

Table 3 Top 10 institutions by number of publications

Rank	Institution	Publications (n)
1	University of Pittsburgh	66
2	Harvard University	52
3	Washington University	32
4	Stanford University	25
5	Brigham & Women's Hospital	23
6	Huazhong University of Science & Technology	20
7	Harvard Medical School	19
8	Duke University	18
9	University of California, Los Angeles	18
10	Emory University	18

Table 4 Top 10 institutions for centrality

Rank	Institution	Centrality
1	University of Pittsburgh	0.17
2	Stanford University	0.05
3	Harvard University	0.04
4	Brigham & Women's Hospital	0.04
5	Harvard Medical School	0.04
6	Duke University	0.04
7	University of California, Los Angeles	0.04
8	Emory University	0.04
9	Washington University	0.03
10	Huazhong University of Science & Technology	0.03

**Figure 6** Co-authored visualization map showed that David K. C. Cooper published the most literatures.**Table 5** Top 5 authors by number of publications

Rank	Author	Publications (n)
1	David K. C. Cooper	38
2	Hidetaka Hara	25
3	Hayato Iwase	18
4	David Ayares	17
5	Cassandra Long	10

generated by CiteSpace V software showed that the cooperative relationship between authors was in clusters (*Figure 6*). Further analysis showed that the authors in each cluster were from the same research institution. Data analysis revealed that the top five authors with the most published articles were David K. C. Cooper, Hidetaka Hara, Hayato Iwase, David Ayares, and Cassandra Long (*Table 5*). However, none of the authors achieved a centrality score

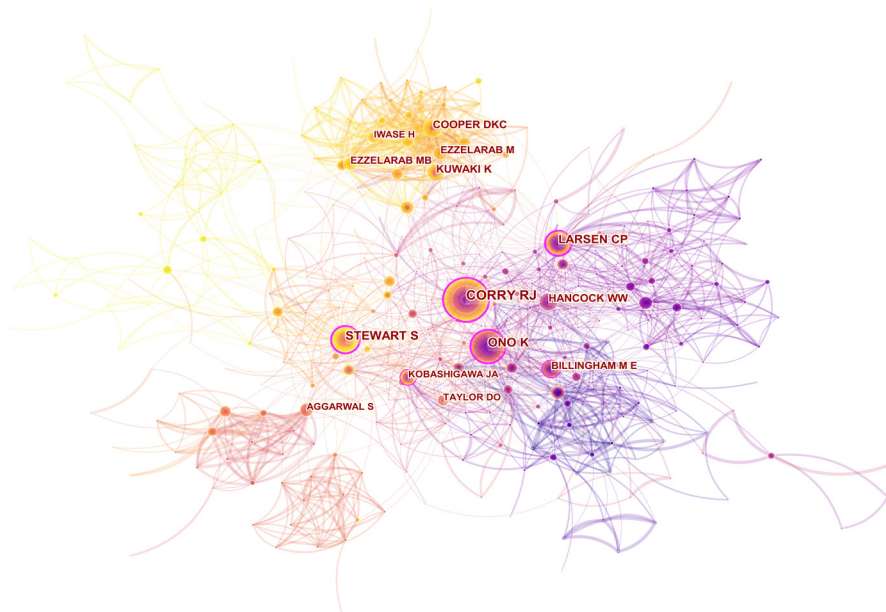


Figure 7 Author co-citation visualization map showed that Robert J. Corry was cited the most.

Table 6 Top 5 authors by frequency of citations

Rank	Author	Citations (n)
1	Robert J. Corry	92
2	Susan Stewart	68
3	Kazuhisa Ono	65
4	Christian P. Larsen	51
5	Kotaro Kuwaki	37

Table 7 Top 5 centrally cited authors

Rank	Authors	Centrality
1	Robert J. Corry	0.33
2	Susan Stewart	0.25
3	Christian P. Larsen	0.25
4	Kazuhisa Ono	0.23
5	Margaret E. Billingham	0.13

of 0.01, indicating less collaboration between authors. The number of co-citations and centrality of the researchers showed that the findings of Robert J. Corry, Susan Stewart, Kazuhisa Ono, and Christian P. Larsen's were most important in this area of research (Figure 7 and Tables 6,7).

Journals

The 1,393 articles retrieved in the present study came from 414 journals, of which 12 had more than 20 publications (Table 8). These journals published 627 articles, accounting for 45.01% of the total literature (Table 8). The top three most cited journals were *Transplantation*, *Journal of Immunology*, and *Proceedings of The National Academy of Sciences of The United States of America* (Table 9). Of the journals cited, *Circulation* and *American Journal of Pathology*

had the highest centrality score (Table 10).

Keywords

CiteSpace V software was used analyze and generate a keyword co-occurrence graph. A total of 152 keywords were used in these literatures, and these keywords generated 1,562 associations in the literature (Figure 8). The five most frequently used keywords were "transplantation", "heart transplantation", "rejection", "immune response," and "expression" (Table 11). The top five keywords by centrality were "transplantation", "heart transplantation", "cardiac transplantation", "tolerance", and "induction" (Table 12). Burst detection of frequently used keywords showed that research hotspots in this field changed over time (Figure 9).

Table 8 Top 12 journals for publications

Journal	Records (n)	Percentages (%)*
<i>Transplantation</i>	159	11.41
<i>Journal of Heart and Lung Transplantation</i>	102	7.32
<i>American Journal of Transplantation</i>	77	5.53
<i>Transplant Immunology</i>	47	3.37
<i>Journal of Immunology</i>	43	3.09
<i>Circulation</i>	42	3.02
<i>Xenotransplantation</i>	32	2.30
<i>Transplant International</i>	29	2.08
<i>Transplantation Proceedings</i>	29	2.08
<i>Current Opinion in Organ Transplantation</i>	24	1.72
<i>Frontiers In Immunology</i>	22	1.58
<i>PLOS One</i>	21	1.51

*, percentages of total number of literatures (n=1,393).

Table 9 Top 10 most cited journals

Rank	Journal	Citations (n)
1	<i>Transplantation</i>	1,058
2	<i>Journal of Immunology</i>	863
3	<i>Proceedings of The National Academy of Sciences of The United States of America</i>	630
4	<i>Journal of Experimental Medicine</i>	604
5	<i>Journal of Clinical Investigation</i>	579
6	<i>Journal of Heart Lung Transplantation</i>	574
7	<i>American Journal of Transplantation</i>	568
8	<i>Circulation</i>	540
9	<i>Nature</i>	520
10	<i>Science</i>	515

Discussion

In the present study, literature in the field of immune response after heart transplantation were searched and statistically analyzed, and an overview of related research was presented. We found that the number of articles in this field did not show a significant year-on-year increase in the number of articles in other fields (13,14). However,

Table 10 Top 10 cited journals for centrality

Rank	Journal	Centrality
1	<i>Circulation</i>	0.10
2	<i>American Journal of Pathology</i>	0.10
3	<i>Circulation Research</i>	0.09
4	<i>Transplantation</i>	0.08
5	<i>Journal of Heart Lung Transplantation</i>	0.07
6	<i>New England Journal of Medicine</i>	0.07
7	<i>Transplant Proceedings</i>	0.07
8	<i>American Journal of Physiology-Heart and Circulation</i>	0.07
9	<i>Proceedings of The National Academy of Sciences of The United States of America</i>	0.06
10	<i>Journal of Clinical Investigation</i>	0.06

the number of citations of these papers showed a significant increasing annual trend. In the analysis of the authors' countries, we found that the USA, China, Germany, and the UK were world leaders in conducting relevant research and cooperation with other countries. US research institutions lead in the research in this field, and authors with more published papers and citations were also mainly from the USA compared with other countries. These findings indicated that the USA leads the world in the field of immune response after heart transplantation. The analysis of journals showed that journals with more publications mainly specialized in transplantation, and journals with more citations included various top comprehensive journals. Keyword analysis showed that research hotspots in this field were investigation of mechanism in recent years.

Since Christiaan Barnard performed the world's first human heart transplant more than 50 years ago, organ transplantation, including heart transplantation, has made significant progress, saving thousands of lives. From 2005 to 2014, the in-hospital survival rate of adult and pediatric heart transplantation in China was 92.7%, and the in-hospital survival rates in 2015 and 2016 were 94.4% and 94.6%, respectively. Postoperative complications and death are closely related to immune rejection after transplantation. Therefore, the immune response which cause graft versus host disease after heart transplantation has always been the focus of basic and clinical research. The use of cyclosporine is a milestone in treatment for graft-versus-host disease after heart transplantation (15). In clinical studies,

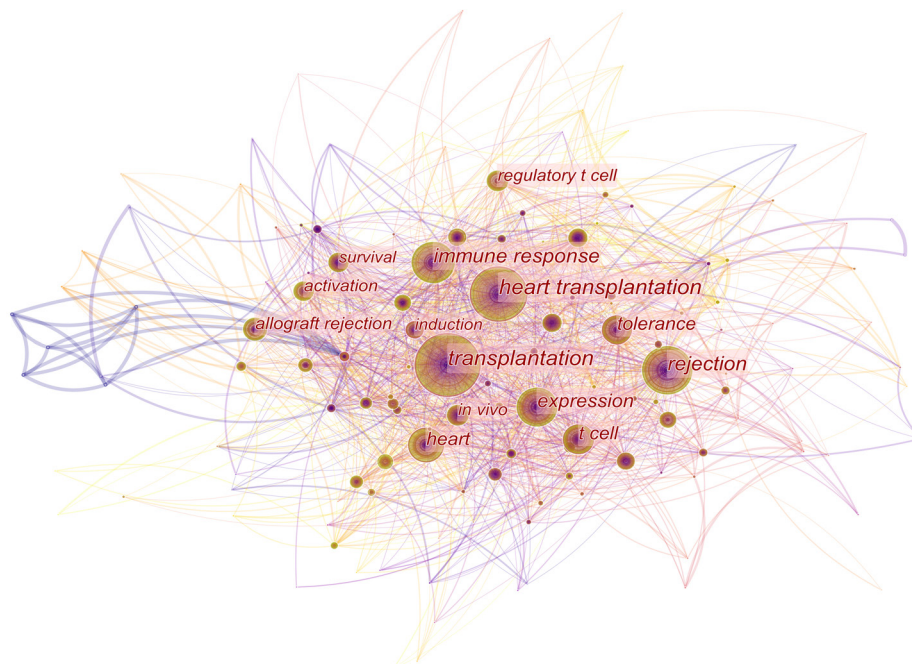


Figure 8 Keyword co-occurrence map showed that “transplantation” was the most used keyword.

Table 11 Top 10 keywords by frequency

Rank	Keywords	Frequency (times)
1	Transplantation	337
2	Heart transplantation	295
3	Rejection	227
4	Immune response	212
5	Expression	164
6	Heart	142
7	T cell	141
8	Tolerance	127
9	Allograft rejection	94
10	Regulatory T cell	87

Table 12 Top 10 keywords by centrality

Rank	Keyword	Centrality
1	Transplantation	0.20
2	Heart transplantation	0.16
3	Cardiac transplantation	0.16
4	Tolerance	0.12
5	Induction	0.12
6	Heart	0.11
7	T cell	0.11
8	Rejection	0.09
9	Immune response	0.09
10	Expression	0.07

immunosuppressive therapy is mainly divided into two steps. The first step is immune induction, and interleukin-2 (IL-2) receptor antagonists are often used. From 2009 to 2016, 52.6% of heart transplantation patients worldwide used antibody drugs for immune induction, among which IL-2 receptor antagonists were the main ones, followed by anti-thymocyte immunoglobulin and anti-lymphocyte immunoglobulin (16). However, immune induction

therapy did not significantly improve the 10-year survival rate of patients, and it was found that certain patients can benefit from immune induction therapy, including younger patients, patients of African descent, patients with severe human leukocyte antigen mismatch, pre-transplantation patients with higher population-reactive antibody levels, and patients with ventricular assist device support (17). The second step is to maintain immunosuppressive

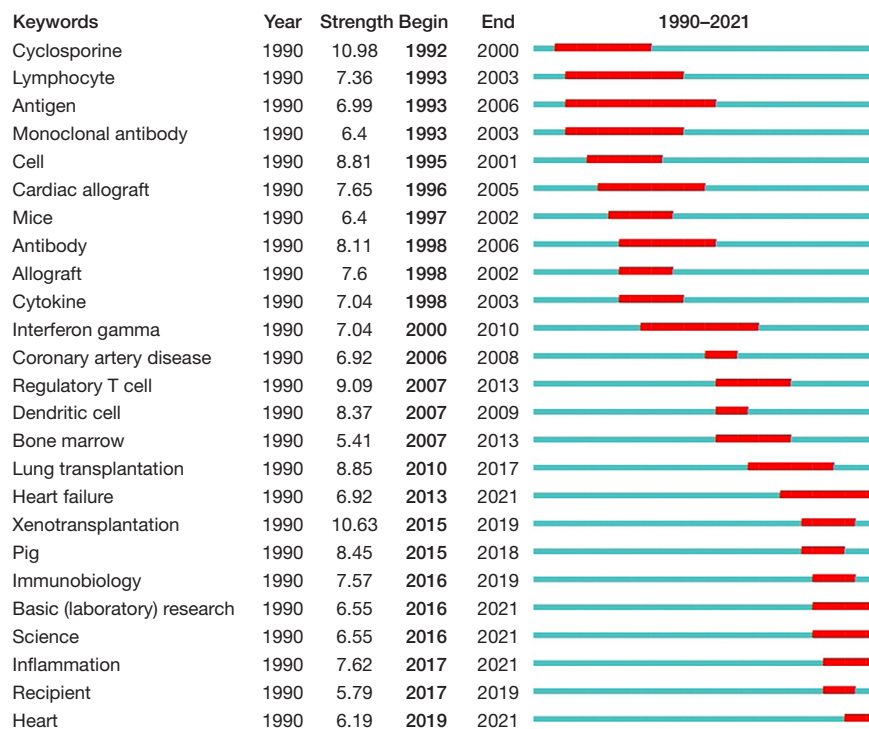


Figure 9 Top 25 keywords with the strongest citation bursts had an annual change of strength.

therapy. Commonly used drugs include tacrolimus, mycophenolate mofetil, corticosteroids, cyclosporine A, sirolimus, and azathioprine. We believe that, in the future, with the development of drug research, especially genetic medication, the prognosis of these patient will be further improved.

There are certain limitations in the study of immune responses after heart transplantation. First, even with the rapid development of medical technology, the number of patients receiving heart transplantations each year is still limited and patients distributed in many countries (18). Second, for the high-risk treatment of heart transplantation, doctors are more cautious about choosing a treatment if evidence is lacking. Third, the cost of conducting such clinical trials is also relatively high. Fourth, the development of immunosuppressive drugs is relatively slow. Therefore, there are relatively few clinical trials on immunosuppressive therapy after heart transplantation. In a relatively large prospective study, 650 patients were randomized to mycophenolate mofetil and azathioprine, in addition to cyclosporine A and corticosteroid treatment. The results showed that the 1-year survival rate was higher in the mycophenolate mofetil group (19). The 3-year follow up showed that mycophenolate mofetil reduced 3-year

mortality and graft loss in heart transplantation patients (20). The results of the present study also found that countries with more heart transplantations have higher centrality scores, indicating that these countries have more external collaboration. Through the cooperation of multiple medical centers in multiple countries, and the increased sample size, the quality of clinical research has been improved.

It can be seen from our research that the related research on immune response after heart transplantation is mainly concentrated in several countries, in particular developed countries in Europe and the USA. This is related to the country's medical and economic levels. However, end-stage heart failure is a worldwide medical problem, and relevant clinical research should include more countries and patients. Moreover, in addition to in-depth basic research, more clinical research is needed to further explore better drugs and programs for the treatment of immune rejection. In conclusion, therapy for modulation of immune response in heart transplantation will be hotspots of research in the future.

Limitations of this study: the bibliometric analysis is mainly used to investigate the general situation of the research in a certain field, and the retrieval results often contain a large number of literatures. It is difficult to

conduct in-depth analysis and induction of each literature, and some important literature could have been missed, particularly early literature. Second, due to the irregular use of keywords in different literature, some keywords could have different word combinations but the same actual meaning, which can cause deviations in the analysis. In addition, due to the limitation of the searched database, documents published in other languages might have been omitted, particularly those in other languages that were not included in the SCI-E database.

Conclusions

Research on immune response after heart transplantation is concentrated in a few countries, and more clinical research is needed in the future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-200/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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