The most influential articles on kidney transplantation
A PRISMA-compliant bibliometric and visualized analysis

Heungman Jun, MD, PhD[a], Ji Woong Hwang, MD, PhD[b, *]

Abstract
Background: Kidney transplantation (KT) has become common in the treatment of end-stage renal disease. However, to date, there have been no bibliometric analyses of KT research to identify the most influential articles. The purpose of this research is to identify and characterize the 100 most cited articles that focus on KT and to clarify the trends in the accomplishments in this field.

Methods: We searched the Thomson Reuters Web of Science citation indexing database and used keyword mapping of VOSviewer. The top 100 most cited manuscripts were analyzed based on their titles, authors, institutions, countries of origin, years of publication, and topics.

Results: The New England Journal of Medicine has published the most manuscripts on kidney transplantation (n = 26) and is the most cited journal (n = 15,642). The United States has the highest number of publications (n = 61). Kashika is the corresponding author with the most published papers (n = 26; 2892 citations). The most common topics of publication are immunosuppressant (n = 34), clinical outcome (n = 26), and pathology (n = 22). Keywords related to immunosuppressant are the most common in keyword mapping with VOSviewer.

Conclusions: This bibliometric analysis of KT research provides the research characteristics and publication trends of this topic. In KT research, immunosuppressants and post-transplant clinical outcomes have been important topics.

Abbreviations: KT = kidney transplantation, LT = liver transplantation, T100 = 100 most cited articles, WoS = Web of Science.

Keywords: bibliometrics, immunosuppressive agents, kidney transplantation

1. Introduction
Kidney transplantation (KT) has become common as an alternative treatment in patients with end-stage renal disease.[1] KT, which was implemented approximately 50 years ago, has improved long-term results with the development of immunosuppressants.[2] Donors, including living and deceased, are needed for KT. Immunosuppressants have been developed for graft survival, and pathology has been further developed for the diagnosis of kidney grafts sensitive to immune conditions. In particular, research on KT is focused on rejection, pathology, and immunosuppressants.

Bibliometric analysis is used to identify publication trends, including authorships, years of publication, countries, and topics in a particular field.[11] It aims to determine research themes that have been most influential in developing the understanding and management of a field. The degree of intellectual impact of a publication can be identified through the list of citation rankings.[4] Using citation ranking, many medical researchers have identified and analyzed the most influential articles in various medical fields, such as orthopedic surgery,[15] plastic surgery,[6] and oncology.[7] However, to date, there have been no bibliometric analyses of KT research to identify the most influential articles. The purpose of this research is to identify and characterize the 100 most cited articles (T100) that focus on KT and clarify the trends in the accomplishments in this field.

2. Methods
The Institutional Review Board approved the review of medical articles using a publicly available database (Ilsan Paik Hospital Institutional Review Board No. 2021-04-030). A search of the Thomson Reuters Web of Science (WoS) citation indexing database was completed (1983–2019) using the following search terms: “kidney transplant*,” “renal transplant*,” “kidney allograft*,” “renal allograft*,” “kidney graft*,” and “renal graft*.” The search was conducted on a single day, April 20,
2020, to prevent changes in the number of citations as much as possible. Articles other than original or review articles were excluded, and only articles written in English were included. All articles were sorted by the number of citations, based on a method initially developed by Paladugu et al[9]; the title and abstract of each article were thoroughly read and evaluated for inclusion by 2 independent reviewers (JWH and HJ) to ensure their relevance to KT. Because only the characteristics of KT needed to be analyzed, studies involving other transplantations, such as liver and pancreas transplantation, were excluded, even though KT was included. Animal studies were also included if the study was performed for renal allografts.

The selected T100 were then evaluated further according to the following parameters: year of publication, country of origin, institution, authorship, journal, number of citations, and article topic. Since a potential bias in this type of study is that older manuscripts have had more time to be cited, the citation rate was analyzed by dividing the number of citations by the number of years since publication. If the number of publications was the same, the ranking was determined based on the total number of citations.

All articles were analyzed according to their topic: immunosuppressant, clinical outcome, pathology, graft outcome, and donor. The “clinical outcome” group included post-transplant diabetes, infection, cancer, quality of life, medication adherence, and practice guideline. The “pathology” group included pathologic, immunologic, and molecular studies about post-transplant allograft nephropathy and included the diagnostic classification such as Banff. The “graft outcome” group included graft survival, graft rejection, and graft function. The “donor” group included management of living and deceased donors and operative graft perfusion in KT.

VOSviewer version 1.6.15 software (Leiden University, Leiden, Netherlands) was used to analyze the relationship between the keywords to generate a map and cluster visualization. In the network visualization, each circle represented a keyword, and the size of circles represented the frequency of occurrence. Larger circles indicate that the keywords appear more frequently. The circle color on the map indicates the cluster to which the keyword belongs. The line between each circle indicates that the keywords are connected, and the length of the line represents the degree of the relationship. Overlay visualization reveals a changing trend of keywords as time progresses by representing the color of each circle. The blue color represents that the timing of keyword appearance is earlier, and the red color represents that the timing is later. Before performing the analysis, keywords were manually standardized by the authors because different expressions of the same keywords may lead to errors in the results.

### 3. Results

The WoS database search returned 93,167 full manuscript publications. Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A843 lists the T100. The number of citations ranged from 2418 for Racusen et al (“The Banff 97 working classification of renal allograft pathology”) to 363 for Colvin et al (“Antibody-mediated renal allograft rejection: Diagnosis and pathogenesis”). The mean number of citations for all articles was 586.4±284.9. The citation rate was the highest for the article “Banff 07 classification of renal allograft pathology: Updates and future directions” by Solez et al. Although the citation rate was applied to prevent time bias, the citation rate of each article was not quite different from its citation numbers, as shown in Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A843.

The T100 are published between 1983 and 2013. The years with the highest number of publications are 1999 and 2000, with a total of 10 papers. The oldest article on the T100, which discusses the Epstein–Barr virus-induced B-cell lymphoproliferative disease after KT, was published in 1983. The most recent article, “Complement-binding anti-HLA antibodies and kidney-allograft survival” was published in 2013.

The T100 are published in 15 journals (Table 1). The New England Journal of Medicine has published the highest number of articles (n = 26; 15,642 citations), followed by Transplantation (n = 24; 12,883 citations). Half of the T100 are published in the 2 aforementioned journals. The highest number of contributions comes from the United States (n = 61), followed by Canada (n = 11) and France (n = 5) (Fig. 1). Although the United States has published more than half of the T100, the institution that has published the highest number of articles is University Alberta in Canada (Table 2). Seven corresponding authors have more than 3 papers on the T100. Kasikse and Meier–Kriesche have the highest number of articles on the T100 (n = 5) (Table 3).

The primary subject matter of the articles is categorized as follows: immunosuppressant, clinical outcome, pathology, graft outcome, and donor (Fig. 2). The most studied topic in publications on KT is “Immunosuppressant” (n = 31), followed by “Clinical outcome” (n = 25) and “Pathology” (n = 20). Throughout the period, the topic of “Clinical outcome” has been continuously studied. Studies on “Pathology” have increased since 1991, and the studies of “Immunosuppressant” have increased significantly since 1996. Figure 2 shows the topical trend of the T100 over a 5-year period from 1981 to 2015. Author-selected keywords of the T100 were analyzed through a co-occurrence network analysis tool using VOSviewer. A total of 106 keywords were extracted from the T100, with a total frequency of 137 (Table S2, Supplemental Digital Content, http/
links.lww.com/MD2/A844). In the network visualization, the highest frequency of occurrence is kidney transplantation (n = 8), followed by graft survival (n = 6) and antibody-mediated rejection (n = 4). Figure 3A is a network formed by 106 keywords and 898 links; it is divided into 5 clusters: red, green, blue, yellow, and purple. The red cluster is the largest, consisting of 32 keywords, including kidney, transplantation, mycophenolate-mofetil, tacrolimus, sirolimus, and cyclosporine. The green and blue clusters are the second largest, with 20 and 17 keywords, respectively. The yellow cluster has 12 keywords, and the purple cluster has 9 keywords. The green cluster includes keywords such as survival, transplantation, and cyclosporine. The blue cluster includes keywords such as rejection, antibody-mediated, and cyclosporine. The yellow cluster includes keywords such as infection, rejection, and cyclosporine. The purple cluster includes keywords such as rejection, antibody-mediated, and cyclosporine.

**Table 2**

Institutions with 3 or more articles in the top 100.

| Institution                        | Country | Number of publications in top 100 | Total number of citations |
|------------------------------------|---------|----------------------------------|---------------------------|
| University of Alberta              | Canada  | 7                                | 5420                      |
| Massachusetts General Hospital     | US      | 7                                | 3261                      |
| University of Michigan             | US      | 6                                | 3033                      |
| University of Florida              | US      | 5                                | 2623                      |
| University of Minnesota            | US      | 5                                | 2447                      |
| Johns Hopkins University           | US      | 3                                | 3649                      |
| University Hospital of Basel       | Switzerland | 3                           | 1810                      |
| University of Texas                | US      | 3                                | 1544                      |

**Table 3**

Corresponding authors with 3 or more articles in the top 100.

| Rank | Author          | Number of publications in top 100 | Total number of citations |
|------|-----------------|----------------------------------|---------------------------|
| 1    | Kasiske, BL     | 5                                | 2892                      |
| 2    | Meier-Kriesche, HU | 5               | 2623                      |
| 3    | Halloran, PF    | 4                                | 2480                      |
| 4    | Hirsch, HH      | 3                                | 1810                      |
| 4    | Kahan, BD       | 3                                | 1544                      |
| 4    | Port, FK        | 3                                | 1403                      |
| 4    | Colvin, RB      | 3                                | 1131                      |
cluster includes 20 keywords, mainly related to kidney transplantation, graft survival, waiting list, and era effect. The blue cluster consists of 18 keywords, mainly antibody-mediated rejection, kidney transplants, dialysis, end-stage renal disease, nonadherence, and donor-specific antibody. The yellow cluster includes 16 keywords, mainly malignancies, immunosuppression, and cardiovascular disease. The purple cluster is the smallest cluster with 15 keywords, mainly about acute rejection, Banff, acute allograft rejection, and acute cellular rejection.

In the overlay visualization, keywords related to transplantation (average published year, 2000) or graft survival (average published year; 2004) in the T100 appear in the early phase (Fig. 3B). However, recently, keywords related to immunosuppression (average published year, 2009) or antibody-mediated rejection (average published year, 2010) have appeared. Notably, keywords of transplantation-related diseases, such as malignancies or cardiovascular disease have appeared in recent years.

4. Discussion
Bibliometric analysis is used to identify publication trends and has been used in various fields.[3] Only in the field of solid organ transplantation, the bibliometric analyses of overall transplantation,[17] liver transplantation (LT),[18] and heart transplantation[19] have been sequentially published since 2014. Unfortunately, there have been no previous bibliometric studies on KT fields. To the best of our knowledge, this is the first bibliometric study to evaluate the subspecialty of KT. In the research topics, there are differences between LT and KT. In the T100 on LT, there are many studies on donors, including allocation, and surgery, including preservation and size mismatching.[18] The T100 on KT are mainly focused on immunology and clinical aspects rather than surgery. Robotic KT has become more common in KT surgery, and research on robotic KT is also being active.[20]

An important theme in the history of KT is the introduction of innovative surgery and the development of immunosuppressants. The first human KT was performed with a deceased donor in 1933 by Voronoy. Although the result of the graft was not good, it is a pioneer surgery in the history of clinical KT. This historical event is first reported in a Spanish journal in 1936.[21] A successful KT was reported in identical twins in 1955 by Murray, which won him the Nobel Prize in 1990.[22] In 1962, the first useful immunosuppressants including azathioprine and 6-mercaptopurine were used in a KT from a deceased donor.[23] Since then, the combination of azathioprine and corticosteroid has become the standard immunosuppressant treatment.[24] Antilymphocyte globulin, consisting of polyclonal antibodies
Figure 3. Keyword co-occurrence analysis of the 100 most cited articles on kidney transplantation. (A) Keyword co-occurrence network visualization of the 100 most cited articles. Each circle represents a keyword, and the size of the circles represents the frequency of occurrence. Larger circles indicate that the keyword appears more frequently. Keywords included in the same cluster are displayed in the same color. The distance between the 2 circles shows the degree of the relationship. (B) Keyword co-occurrence overlay visualization. The color of the circle represents the average year of publication, from blue (distant year) to red (last year).
obtained from various animals, is used as an adjuvant. In the 1980s, the combinations of cyclosporin improved the results of KT. FK 506, discovered in 1984, is now widely used as a standard immunosuppressant in KT. Since then, various immunosuppressants have been introduced more rapidly, thus improving KT results. Recently, due to the shortage of kidney allografts, interest in and research on expanded criteria donors, including elderly deceased and high Kidney Donor Risk Index donors, has increased. For the best preservation of kidney allografts, many studies such as hypothermic machine perfusion and donor pretreatment are being conducted.

VOSviewer analyzes large-scale bibliographic data and the relationships between keywords selected by authors in their own publications and cluster publications based on direct citation relations. It also shows the time trend of keyword changes to inform the progress of the research field. In a recent bibliometric analysis, trend analysis was diversified through the keyword mapping methods of VOSviewer. The keywords presented in the T100 on KT are mainly distributed in 5 clusters: transplantation, graft survival, immunosuppressant, rejection, and post-transplant clinical outcome. Interestingly, keyword analysis through VOSviewer shows that keywords such as “malignancy” or “cardiovascular diseases,” which are complications that can occur after KT, have emerged relatively recently, along with the long history of KT. Expanded criteria donor, graft preservation, and immune tolerance, which have recently been increasing interest in transplantation, were not included as keywords. Although there are many topics related to transplantation, it is difficult to clearly classify them as studies on KT. The authors thought that the artificial classification by the authors could induce another bias.

As in many previous bibliometric analyses, our study has some limitations. First, only 1 database was used in our study as a reference source. This can result in the omission of articles not recognized by WoS, although it is the largest bibliometric database currently available. Second, influential recent articles were rarely included in our study because they might need the time to accumulate citations. Lastly, although a significant portion of the literature was not written in English, articles in languages other than English were not included in our database.

5. Conclusions
This bibliometric analysis of KT research provides the research characteristics and publication trends of this topic. In KT research, immunosuppressants and post-transplant clinical outcomes have been important topics.

Author contributions
Conceptualization: Ji Woong Hwang.
Data curation: Heungman Jun, Ji Woong Hwang.
Formal analysis: Heungman Jun.
Visualization: Ji Woong Hwang.
Writing – original draft: Heungman Jun, Ji Woong Hwang.
Writing – review & editing: Heungman Jun, Ji Woong Hwang.

References
[1] Suthanthiran M, Strom TB. Renal transplantation. N Engl J Med 1994;331:365–76.
[2] Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999;341:1725–30.
[3] Luukkonen T. Bibliometrics and evaluation of research performance. Ann Med 1990;22:145–50.
[4] Murray MR, Wang T, Schroeder GD, Hsu WK. The 100 most cited spine articles. Eur Spine J 2012;21:1049–59.
[5] Kelly JC, Glyn RN, O’Brien DE, Felle P, McCabe JP. The 100 classic papers of orthopaedic surgery: a bibliometric analysis. J Bone Joint Surg Br 2010;92:1338–43.
[6] Shah E, Heiman AJ, Ricci JA. Analysis of alternative metrics of research impact: a correlation comparison between altmetric attention scores and traditional bibliometrics among plastic surgery research. Plast Reconstr Surg 2020;146:664–70.
[7] Aln SK, Hwang JW. Global trends in immunotherapy research on breast cancer over the past 10 years. J Oncol 2020;2020:4708394.
[8] Paladugu R, Schein M, Gardezi S, Wise L. One hundred citation classics in general surgical journals. World J Surg 2002;26:1099–105.
[9] van Eek NJ, Walmant L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrica 2010;84:523–38.
[10] Cao M, Wang L, Zhang L, Duan J. Global publication trends and hotspots of molecular biomarkers in DILI from 1991 to 2020: a 30-year bibliometric analysis. Sci Prog 2021;104:368504211000535.
[11] Romero I, Portillo-Salido E. Trends in sigma-1 receptor research: a 25-year bibliometric analysis. Front Pharmacol 2019;10:564.
[12] Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int 1999;55:713–23.
[13] Colvin RB. Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. J Am Soc Nephrol 2007;18:1046–56.
[14] Solez K, Colvin RB, Racusen LC, et al. Banff 07 classification of renal allograft pathology: updates and future directions. Am J Transplant 2008;8:733–60.
[15] Hanto DW, Gaj-Peczalska KJ, Frizza GA, et al. Epstein-Barr virus (EBV)-induced polyclonal and monoclonal B-cell lymphoproliferative diseases occurring after renal transplantation. Clinical, pathologic, and virologic findings and implications for therapy. Ann Surg 1983;198:356–69.
[16] Loupy A, Lefaucheur C, Vernerey D, et al. Complement-binding anti-HLA antibodies and kidney-allograft survival. N Engl J Med 2013;369:1215–26.
[17] O’Sullivan K, Hurley JP. The 100 most cited publications in transplantation. Ann Transplant 2014;19:436–43.
[18] Ozbilgin M, Unek T, Egeli T, et al. The most frequently cited 100 articles in liver transplantation literature. Transplant Proc 2017;49:551–61.
[19] Kolkah AA, Fugar S, Vondee N, et al. Bibliometric analysis of the top 100 most cited articles in the first 50 years of heart transplantation. Am J Cardiol 2019;123:175–86.
[20] Tzvetanov IG, Spaggiari M, Tulla KA, et al. Robotic kidney transplantation in the obese patient: 10-year experience from a single center. Am J Transplant 2020;20:430–40.
[21] Matevosian K, Kern H, Huser N, et al. Surgeon Yuri Voronoy (1895–1961)– a pioneer in the history of clinical transplantation: in memoriam at the 75th anniversary of the first human kidney transplantation. Transpl Int 2009;22:1132–9.
[22] Stefoni S, Camps-Mercader J, Donati G, Orlandi V. The history of clinical renal transplant. J Nephrol 2004;17:475–8.
[23] Murray JE, Merrill JP, Harrison JJH, Wilson RE, Dammin GJ. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. N Engl J Med 1963;268:1315–23.
[24] Starzl TE, Marchioro TL, Waddell WR. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 1963;117:385–95.
[25] Starzl TE, Marchioro TL, Porter KA, Iwasaki Y, Cerilli GJ. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation and in human renal homotransplantation. Surg Gynecol Obstet 1967;124:301–8.
[26] Calne RY, Rolles K, White DJ, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979;2:1033–6.
[27] Starzl TE, Todo S, Fung J, Demetris AJ, Venkataramman R, Jain A, FK 506 for liver, kidney, and pancreas transplantation. Lancet 1989;2:1000–4.
[28] Jun H, Kim YH, Kim JK, et al. Outcomes of kidney transplantation from elderly deceased donors of a Korean registry. PLoS One 2020;15: e0232177.
[29] O’Callaghan JM, Morgan RD, Knight SR, Morris PJ. Systemic review and meta-analysis of hypothermic machine perfusion versus static cold

Jun and Hwang Medicine (2022) 101:3
storage of kidney allografts on transplant outcomes. Br J Surg 2013; 100:991–1001.
[30] van Eck NJ, Waltman L. Citation-based clustering of publications using CitNetExplorer and VOSviewer. Scientometrics 2017;111: 1053–70.
[31] Xu L, Tang F, Wang Y, et al. Research progress of pre-hospital emergency during 2000-2020: a bibliometric analysis. Am J Transl Res 2021;13:1109–24.
[32] Seglen PO. Citation rates and journal impact factors are not suitable for evaluation of research. Acta orthop scand 1998;69:224–9.