Bibliometric Analysis of the Top 100 Most Cited Articles in the First 50 Years of Heart Transplantation

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The world celebrates over 50 years since the first human-to-human heart transplant. Bibliometric analysis is a statistical concept that has recently evolved, enabling scientists to study citation patterns and identify characteristics of highly cited scholarly work in different fields. Although it has been widely utilized, such analyses have not been conducted to date on heart transplant literature. We sought to assess the characteristics of the top 100 most referenced citations in the field of heart transplantation. We searched the Scopus database (www.scopus.com) to identify all articles relating to heart transplantation. The articles were arranged in descending order from most cited to least cited and selected articles were scrutinized for data extraction. One hundred articles were included in the final list. Of the total 40,660 citations identified, 3,210 (8.0%) were self-citations, which impacted the final rank order. The articles were published in 25 different journals between 1960 and 2013. The most productive 5-year time period was between 2000 and 2005, when 24 of the 100 most cited publications were produced. There was no correlation between the journals' impact factors and the number of articles produced per journal. The presence and type of funding were not associated with the number of citations. Over 85% of first and senior investigators were men. In conclusion, our study highlights key features of the most highly cited scientific literature on heart transplantation and provides insights into trends of published work in this field. Additionally, this work may serve as a useful guide to researchers and funding bodies by highlighting the most prolific areas of cardiac transplant research to date. Published by Elsevier Inc. (Am J Cardiol 2019;123:175−186)

The world celebrates over 50 years since Dr. Christiaan Barnard, a renowned South African cardiac surgeon, revolutionized the field of cardiac surgery for patients with heart failure. It was on December 3, 1967 at Groote Schuur Hospital in Cape Town, South Africa, when Dr. Barnard's scalpel incised into the chest of the 53-year-old South African grocer, Lewis Washkansky, to transplant the heart of Denise Darvall, a 25-year-old woman who had sustained fatal injuries in a car accident, marking the first ever human-to-human heart transplantation.[1−6] In celebration of passing this 50-year milestone, it is apropos to reflect on this fascinating, transformative surgical procedure that has touched the hearts of many, with a focus on the relevant body of literature that has been published in this particular area of medicine. Bibliometric analysis is a statistical concept that has evolved over the past few decades, enabling scientists to study citation patterns and identify characteristics of highly cited scholarly work in different fields.[7,8] While it has been utilized in a wide spectrum of specialties, such analyses have not been conducted on heart transplant literature to date.[9−12] We sought to assess the characteristics of the top 100 most highly referenced citations in the field of heart transplantation. In addition to highlighting the most prolific areas of research in this field, our study also intends to serve as a tribute to those who helped humanity achieve and sustain such an incredible milestone.

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See page 185 for disclosure information.

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Methods

We searched the Scopus database (www.scopus.com) to identify all articles relating to heart transplant. To enhance our search sensitivity, 2 independent reviewers (AK and SF) reviewed the literature for relevant articles, including clinical trials and systematic reviews in the field of heart transplant, and identified the most commonly used search terms. The search strategy used in the fields of title,

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Table 1
Top 100 original articles in the field of heart transplantation.

Rank	Article	All citations	No self-citations	Citations-per-year*
1	Ono K, Lindsey ES. Improved technique of heart transplantation in rats. *J Thorac Cardiovasc Surg* 1969;57:225−229	1376	1372	28
2	Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;83:778−786	1164	1116	43
3	Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, Chia D, Terasaki PI, Sabad A, Cogert GA, Trosian K, Hamilton MA, Moriguchi JD, Kawata N, Hage A, Drinkwater DC, Stevenson LW. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 1995;333:621−627.	1067	1014	43
4	Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, MacGillivray TE, Farrar DJ, Frazier OH, HeartMate IICI. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;357:885−896.	1057	871	96
5	Quaini F, Urbanek K, Beltrami AP, Finato N, Beltrami CA, Nadal-Ginard B, Kajstura J, Leri A, Anversa P. Chimerism of the transplanted heart. *N Engl J Med* 2002;346:5−15.	1013	955	63
6	Klug MG, Soonpaa MH, Koh GY, Field LJ. Genetically selected cardiomyocytes from differentiating embronic stem cells form stable intracardiac grafts. *J Clin Invest* 1996;98:216−224.	900	875	41
7	Eisen HJ, Tuzcu EM, Dorent R, Kobashigawa J, Mancini D, Valantine-von Kaeppler HA, Starling RC, Sorensen K, Hummel M, Lind JM, Abeywickrama KH, Bernhardt P, Group RBS. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003;349:847−858.	856	750	57
8	Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997;95:2660−2667.	832	795	40
9	Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. *JAMA* 1989;261:3561−3566.	755	744	26
10	Swinnen LJ, Costanzo-Nordin MR, Fisher SG, O'Sullivan EJ, Johnson MR, Heroux AL, Dizikes GJ, Pifarre R, Fisher RI. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. *N Engl J Med* 1990;323:1723−1728.	746	723	26
11	Corry RJ, Winn HJ, Russell PS. Primarily vascularized allografts of hearts in mice. The role of H-2D, H-2K, and non-H-2 antigens in rejection. *Transplantation* 1973;16:343−350.	711	683	16
12	Shimizu T, Yamato M, Isoi Y, Akutsu T, Setomaru T, Abe K, Kikuchi A, Umezu M, Okano T. Fabrication of pulsatile cardiac tissue grafts using a novel 3-dimensional cell sheet manipulation technique and temperature-responsive cell culture surfaces. *Circ Res* 2002;90:e40.	645	484	40
13	Isobe M, Yagita H, Okumura K, Ihara A. Specific acceptance of cardiac allograft after treatment with antibodies to ICAM-1 and LFA-1. *Science* 1992;255:1125−1127	642	567	25
14	Zhang M, Methot D, Poppa V, Fujio Y, Walsh K, Murry CE. Cardiomyocyte grafting for cardiac repair: graft cell death and anti-death strategies. *J Mol Cell Cardiol* 2001;33:907−921	616	596	36
15	Zimmermann WH, Melnychenko I, Wasmeier G, Didie M, Naito H, Nixdorff U, Hess A, Budinsky L, Brune K, Michaelis B, Dhein S, Schwoerer A, Ehmke H, Eschenhagen T. Engineered heart tissue grafts improve systolic and diastolic function in infarcted rat hearts. *Nat Med* 2006;12:452−458.	586	526	49
16	Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, Fauchald P, Simonsen S. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol* 1999;40:177−186.	575	569	30
17	Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, Conte JV, Bogaev RC, MacGillivray TE, Naka Y, Mancini D, Massey HT, Chen L, Klodell CT, Aranda JM, Moazami N, Ewald GA, Farrar DJ, Frazier OH, HeartMate III. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol* 2009;54:312−321.	563	452	53
18	Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* 1993;342:1514−1516.	538	529	22
19	Ruschitzka F, Meier PJ, Turina M, Luscher TF, Noll G. Acute heart transplant rejection due to Saint John's wort. *Lancet* 2000;355:548−549.	528	524	29
20	Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, Stinson EB, Shumway NE. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. *N Engl J Med* 1982;306:557−564.	487	441	14
21	Barnard CN. The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. *South African Medical Journal* 1967;41:1271−1274.	481	479	9

(*continued*)

Table 1 (***Continued***)

Rank	Article	All citations	No self-citations	Citations-per-year*
22	Myers BD, Sibley R, Newton L, Tomlanovich SJ, Boshkos C, Stinson E, Luetscher JA, Whitney DJ, Krasny D, Coplon NS, Perlroth MG. The long-term course of cyclosporine-associated chronic nephropathy. *Kidney Int* 1988;33:590−600.	479	474	16
23	Soonpaa MH, Koh GY, Klug MG, Field LJ. Formation of nascent intercalated disks between grafted fetal cardiomyocytes and host myocardium. *Science* 1994;264:98−101.	470	428	20
24	Kobashigawa J, Miller L, Renlund D, Mentzer R, Alderman E, Bourge R, Costanzo M, Eisen H, Dureau G, Ratkovec R, Hummel M, Ipe D, Johnson J, Keogh A, Mamelok R, Mancini D, Smart F, Valantine H. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Mycophenolate Mofetil Investigators. *Transplantation* 1998;66:507−515.	455	371	23
25	Schuler W, Sedrani R, Cottens S, Haberlin B, Schulz M, Schuurman HJ, Zenke G, Zerwes HG, Schreier MH. SDZ RAD, a new rapamycin derivative: pharmacological properties in vitro and in vivo. *Transplantation* 1997;64:36−42.	454	434	22
26	Larsen CP, Morris PJ, Austyn JM. Migration of dendritic leukocytes from cardiac allografts into host spleens. A novel pathway for initiation of rejection. *J Exp Med* 1990;171:307−314.	450	403	16
27	Lin H, Bolling SF, Linsley PS, Wei RQ, Gordon D, Thompson CB, Turka LA. Long-term acceptance of major histocompatibility complex mismatched cardiac allografts induced by CTLA4Ig plus donor-specific transfusion. *J Exp Med* 1993;178:1801−1806.	450	430	18
28	Uretsky BF, Murali S, Reddy PS, Rabin B, Lee A, Griffith BP, Hardesty RL, Trento A, Bahnson HT. Development of coronary artery disease in cardiac transplant patients receiving immunosuppressive therapy with cyclosporine and prednisone. *Circulation* 1987;76:827−834.	447	439	14
29	Leor J, Aboulafia-Etzion S, Dar A, Shapiro L, Barbash IM, Battler A, Granot Y, Cohen S. Bioengineered cardiac grafts: A new approach to repair the infarcted myocardium? *Circulation* 2000;102: III56−61.	415	379	23
30	Wenke K, Meiser B, Thiery J, Nagel D, von Scheidt W, Steinbeck G, Seidel D, Reichart B. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. *Circulation* 1997;96:1398−1402.	413	397	20
31	Reinecke H, Zhang M, Bartosek T, Murry CE. Survival, integration, and differentiation of cardiomyocyte grafts: a study in normal and injured rat hearts. *Circulation* 1999;100:193−202.	413	385	22
32	Hancock WW, Buelow R, Sayegh MH, Turka LA. Antibody-induced transplant arteriosclerosis is prevented by graft expression of anti-oxidant and anti-apoptotic genes. *Nat Med* 1998;4:1392 −1396.	408	343	20
33	Platt JL, Fischel RJ, Matas AJ, Reif SA, Bolman RM, Bach FH. Immunopathology of hyperacute xenograft rejection in a swine-to-primate model. *Transplantation* 1991;52:214−220.	408	303	15
34	Frazier OH, Rose EA, Oz MC, Dembitsky W, McCarthy P, Radovancevic B, Poirier VL, Dasse KA, HeartMate LILVAS. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. *J Thorac Cardiovasc Surg* 2001;122:1186−1195.	392	323	23
35	Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. *Surg Forum* 1960;11:18−19.	386	376	8
36	Pagani FD, DerSimonian H, Zawadzka A, Wetzel K, Edge AS, Jacoby DB, Dinsmore JH, Wright S, Aretz TH, Eisen HJ, Aaronson KD. Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation. *J Am Coll Cardiol* 2003;41:879−888.	383	374	26
37	Trulock EP, Christie JD, Edwards LB, Boucek MM, Aurora P, Taylor DO, Dobbels F, Rahmel AO, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart-lung transplantation report-2007. *J Heart Lung Transplant* 2007;26:782−795.	383	368	35
38	Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official report−1999. *J Heart Lung Transplant* 1999;18:611−626.	371	369	20
39	Costanzo MR, Naftel DC, Pritzker MR, Heilman JK, 3rd, Boehmer JP, Brozena SC, Dec GW, Ventura HO, Kirklin JK, Bourge RC, Miller LW. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. *J Heart Lung Transplant* 1998;17:744−753.	368	349	18
40	Laflamme MA, Myerson D, Saffitz JE, Murry CE. Evidence for cardiomyocyte repopulation by extracardiac progenitors in transplanted human hearts. *Circ Res* 2002;90:634−640.	362	353	23
41	Scherrer U, Vissing SF, Morgan BJ, Rollins JA, Tindall RS, Ring S, Hanson P, Mohanty PK, Victor RG. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990;323:693−699.	362	348	13
42	Xue T, Cho HC, Akar FG, Tsang SY, Jones SP, Marban E, Tomaselli GF, Li RA. Functional integration of electrically active cardiac derivatives from genetically engineered human embryonic	360	307	28

(*continued*)

Table 1 (***Continued***)

Rank	Article	All citations	No self-citations	Citations-per-year*
	stem cells with quiescent recipient ventricular cardiomyocytes: insights into the development of cell-based pacemakers. *Circulation* 2005;111:11−20			
43	St Goar FG, Pinto FJ, Alderman EL, Valantine HA, Schroeder JS, Gao SZ, Stinson EB, Popp RL. Intracoronary ultrasound in cardiac transplant recipients. In vivo evidence of "angiographically silent" intimal thickening. *Circulation* 1992;85:979−987.	342	314	13
44	Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Hertz MI, International Society of H, Lung T. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. *J Heart Lung Transplant* 2012;31:1073−1086.	337	324	56
45	Taylor DO, Edwards LB, Aurora P, Christie JD, Dobbels F, Kirk R, Rahmel AO, Kucheryavaya AY, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report−2008. *J Heart Lung Transplant* 2008;27:943−956.	331	323	33
46	Bando K, Paradis IL, Similo S, Konishi H, Komatsu K, Zullo TG, Yousem SA, Close JM, Zeevi A, Duquesnoy RJ, Manzetti J, Keenam RG, Armitage JM, Hardesty RL, Griffith BP. Obliterative bronchiolitis after lung and heart-lung transplantation. An analysis of risk factors and management. *J Thorac Cardiovasc Surg* 1995;110:4−13; discussion 13−14.	330	312	14
47	Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, Dobbels F, Kirk R, Rahmel AO, Hertz MI, International Society of H, Lung T. The Registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report−2012. *J Heart Lung Transplant* 2012;31:1052−1064.	327	309	55
48	Fu F, Li Y, Qian S, Lu L, Chambers F, Starzl TE, Fung JJ, Thomson AW. Costimulatory molecule-deficient dendritic cell progenitors (MHC class II+, CD80dim, CD86-) prolong cardiac allograft survival in nonimmunosuppressed recipients. *Transplantation* 1996;62:659−665.	320	282	23
49	Copeland JG, Smith RG, Arabia FA, Nolan PE, Sethi GK, Tsau PH, McClellan D, Slepian MJ, CardioWest Total Artificial Heart I. Cardiac replacement with a total artificial heart as a bridge to transplantation. *N Engl J Med* 2004;351:859−867.	320	215	15
50	Mancini D, Pinney S, Burkhoff D, LaManca J, Itescu S, Burke E, Edwards N, Oz M, Marks AR. Use of rapamycin slows progression of cardiac transplantation vasculopathy. *Circulation* 2003;108:48−53.	317	272	12
51	Frazier OH, Rose EA, Macmanus Q, Burton NA, Lefrak EA, Poirier VL, Dasse KA. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. *Ann Thorac Surg* 1992;53:1080−1090.	316	307	21
52	Keogh A, Richardson M, Ruygrok P, Spratt P, Galbraith A, O'Driscoll G, Macdonald P, Esmore D, Muller D, Faddy S. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. *Circulation* 2004;110:2694−2700.	315	303	23
53	Pearson TC, Alexander DZ, Winn KJ, Linsley PS, Lowry RP, Larsen CP. Transplantation tolerance induced by CTLA4-Ig. *Transplantation* 1994;57:1701−1706.	311	244	26
54	Deng MC, Eisen HJ, Mehra MR, Billingham M, Marboe CC, Berry G, Kobashigawa J, Johnson FL, Starling RC, Murali S, Pauly DF, Baron H, Wohlgemuth JG, Woodward RN, Klingler TM, Walther D, Lal PG, Rosenberg S, Hunt S, Investigators C. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. *Am J Transplant* 2006;6:150−160.	313	281	13
55	Taylor DO, Stehlik J, Edwards LB, Aurora P, Christie JD, Dobbels F, Kirk R, Kucheryavaya AY, Rahmel AO, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Heart Transplant Report-2009. *J Heart Lung Transplant* 2009;28:1007−1022.	305	296	34
56	Merigan TC, Renlund DG, Keay S, Bristow MR, Starnes V, O'Connell JB, Resta S, Dunn D, Gamberg P, Ratkovec RM, Richenbacher WE, Millar RC, Dumond C, DeAmond B, Sullivan V, Cheney T, Buhles W, Stinson EB. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. *N Engl J Med* 1992;326:1182−1186.	297	290	11
57	Reinecke H, Poppa V, Murry CE. Skeletal muscle stem cells do not transdifferentiate into cardiomyocytes after cardiac grafting. *J Mol Cell Cardiol* 2002;34:241−249.	294	278	18
58	Larsen CP, Alexander DZ, Hollenbaugh D, Elwood ET, Ritchie SC, Aruffo A, Hendrix R, Pearson TC. CD40-gp39 interactions play a critical role during allograft rejection. Suppression of allograft rejection by blockade of the CD40-gp39 pathway. *Transplantation* 1996;61:4−9.	291	268	13
59	Hertz MI, Taylor DO, Trulock EP, Boucek MM, Mohacsi PJ, Edwards LB, Keck BM. The registry of the international society for heart and lung transplantation: nineteenth official report-2002. *J Heart Lung Transplant* 2002;21:950−970.	291	252	49
60	Takeuchi T, Lowry RP, Konieczny B. Heart allografts in murine systems. The differential activation of Th2-like effector cells in peripheral tolerance. *Transplantation* 1992;53:1281−1294.	290	279	18

(*continued*)

Table 1 (***Continued***)

Rank	Article	All citations	No self-citations	Citations-per-year*
61	Armitage JM, Kormos RL, Stuart RS, Fricker FJ, Griffith BP, Nalesnik M, Hardesty RL, Dummer JS. Posttransplant lymphoproliferative disease in thoracic organ transplant patients: ten years of cyclosporine-based immunosuppression. *J Heart Lung Transplant* 1991;10:877−886; discussion 886−877.	288	282	11
62	Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, Jessup ML, Gregoric ID, Loyalka P, Frazier OH, Jeevanandam V, Anderson AS, Kormos RL, Teuteberg JJ, Levy WC, Naftel DC, Bittman RM, Pagani FD, Hathaway DR, Boyce SW, HeartWare Ventricular Assist Device Bridge to Transplant ATI. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation* 2012;125:3191−3200.	286	279	11
63	Li RK, Jia ZQ, Weisel RD, Mickle DA, Choi A, Yau TM. Survival and function of bioengineered cardiac grafts. *Circulation* 1999;100:II63−69.	284	248	41
64	Hammond EH, Yowell RL, Nunoda S, Menlove RL, Renlund DG, Bristow MR, Gay WA, Jr., Jones KW, O'Connell JB. Vascular (humoral) rejection in heart transplantation: pathologic observations and clinical implications. *J Heart Transplant* 1989;8:430−443.	283	271	15
65	Starling RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, Russell SD, Conte JV, Aaronson KD, McGee EC, Jr., Cotts WG, DeNofrio D, Pham DT, Farrar DJ, Pagani FD. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2011;57:1890−1898.	282	248	10
66	Salomon RN, Hughes CC, Schoen FJ, Payne DD, Pober JS, Libby P. Human coronary transplantation-associated arteriosclerosis. Evidence for a chronic immune reaction to activated graft endothelial cells. *Am J Pathol* 1991;138:791−798.	276	233	10
67	Johnson DE, Gao SZ, Schroeder JS, DeCampli WM, Billingham ME. The spectrum of coronary artery pathologic findings in human cardiac allografts. *J Heart Transplant* 1989;8:349−359.	275	223	19
68	West LJ, Pollock-Barziv SM, Dipchand AI, Lee KJ, Cardella CJ, Benson LN, Rebeyka IM, Coles JG. ABO-incompatible heart transplantation in infants. *N Engl J Med* 2001;344:793−800.	272	260	9
69	Michaels PJ, Espejo ML, Kobashigawa J, Alejos JC, Burch C, Takemoto S, Reed EF, Fishbein MC. Humoral rejection in cardiac transplantation: risk factors, hemodynamic consequences and relationship to transplant coronary artery disease. *J Heart Lung Transplant* 2003;22:58−69.	271	256	21
70	Dallman MJ, Larsen CP, Morris PJ. Cytokine gene transcription in vascularised organ grafts: analysis using semiquantitative polymerase chain reaction. *J Exp Med* 1991;174:493−496.	271	217	18
71	Lee I, Wang L, Wells AD, Dorf ME, Ozkaynak E, Hancock WW. Recruitment of Foxp3+ T regulatory cells mediating allograft tolerance depends on the CCR4 chemokine receptor. *J Exp Med* 2005;201:1037−1044.	270	251	10
72	Leventhal JR, Dalmasso AP, Cromwell JW, Platt JL, Manivel CJ, Bolman RM, 3rd, Matas AJ. Prolongation of cardiac xenograft survival by depletion of complement. *Transplantation* 1993;55:857−865; discussion 865−856.	268	247	53
73	Ciubotariu R, Liu Z, Colovai AI, Ho E, Itescu S, Ravalli S, Hardy MA, Cortesini R, Rose EA, Suciu-Foca N. Persistent allopeptide reactivity and epitope spreading in chronic rejection of organ allografts. *J Clin Invest* 1998;101:398−405.	267	244	53
74	Yusen RD, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Kirk R, Lund LH, Rahmel AO, Stehlik J, International Society for H, Lung T. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report−2013; focus theme: age. *J Heart Lung Transplant* 2013;32:965−978.	266	236	24
75	Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report-2000. *J Heart Lung Transplant* 2000;19:909−931.	266	195	11
76	Leor J, Patterson M, Quinones MJ, Kedes LH, Kloner RA. Transplantation of fetal myocardial tissue into the infarcted myocardium of rat. A potential method for repair of infarcted myocardium? *Circulation* 1996;94:II332−336.	262	261	15
77	Herreros J, Prosper F, Perez A, Gavira JJ, Garcia-Velloso MJ, Barba J, Sanchez PL, Canizo C, Rabago G, Marti-Climent JM, Hernandez M, Lopez-Holgado N, Gonzalez-Santos JM, Martin-Luengo C, Alegria E. Autologous intramyocardial injection of cultured skeletal muscle-derived stem cells in patients with non-acute myocardial infarction. *Eur Heart J* 2003;24:2012−2020.	260	242	17
78	Bunde T, Kirchner A, Hoffmeister B, Habedank D, Hetzer R, Cherepnev G, Proesch S, Reinke P, Volk HD, Lehmkuhl H, Kern F. Protection from cytomegalovirus after transplantation is correlated with immediate early 1-specific CD8 T cells. *J Exp Med* 2005;201:1031−1036.	260	234	12
79	Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, Dobbels F, Kirk R, Rahmel AO, Yusen RD, Stehlik J, International Society for H, Lung T. The Registry of the	259	237	20

(*continued*)

Table 1 (***Continued***)

Rank	Article	All citations	No self-citations	Citations-per-year*
	International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report−2013; focus theme: age. *J Heart Lung Transplant* 2013;32:951−964.			
80	Christie JD, Edwards LB, Aurora P, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Taylor DO, Kucheryavaya AY, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Lung and Heart-Lung Transplantation Report-2009. *J Heart Lung Transplant* 2009;28:1031−1049.	254	250	28
81	Gerna G, Zipeto D, Parea M, Revello MG, Silini E, Percivalle E, Zavattoni M, Grossi P, Milanesi G. Monitoring of human cytomegalovirus infections and ganciclovir treatment in heart transplant recipients by determination of viremia, antigenemia, and DNAemia. *J Infect Dis* 1991;164:488−498.	254	221	15
82	Husain S, Alexander BD, Munoz P, Avery RK, Houston S, Pruett T, Jacobs R, Dominguez EA, Tollemar JG, Baumgarten K, Yu CM, Wagener MM, Linden P, Kusne S, Singh N. Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-Aspergillus mycelial fungi. *Clin Infect Dis* 2003;37:221−229.	251	210	17
83	McDonald K, Rector TS, Braulin EA, Kubo SH, Olivari MT. Association of coronary artery disease in cardiac transplant recipients with cytomegalovirus infection. *Am J Cardiol* 1989;64:359−362.	250	247	9
84	Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. *J Am Coll Cardiol* 1992;19:48−54.	249	247	10
85	Schroeder JS, Gao SZ, Alderman EL, Hunt SA, Johnstone I, Boothroyd DB, Wiederhold V, Stinson EB. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. *N Engl J Med* 1993;328:164−170.	248	234	10
86	Burke CM, Theodore J, Dawkins KD, Yousem SA, Blank N, Billingham ME, Van Kessel A, Jamieson SW, Oyer PE, Baldwin JC, Stinson EB, Stinson EB, Shumway NE, Robin ED. Post-transplant obliterative bronchiolitis and other late lung sequelae in human heart-lung transplantation. *Chest* 1984;86:824−829.	248	220	7
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88	Pearce NW, Dorsch SE, Hall BM. Specific unresponsiveness in rats with prolonged cardiac allograft survival after treatment with cyclosporine. IV. Examination of T cell subsets in graft-versus-host assays. *Transplantation* 1990;50:493−497.	245	213	20
89	Blume ED, Naftel DC, Bastardi HJ, Duncan BW, Kirklin JK, Webber SA, Pediatric Heart Transplant Study I. Outcomes of children bridged to heart transplantation with ventricular assist devices: a multi-institutional study. *Circulation* 2006;113:2313−2319.	245	213	9
90	Krieger NR, Yin DP, Fathman CG. CD4+ but not CD8+ cells are essential for allorejection. *J Exp Med* 1996;184:2013−2018.	244	235	11
91	Bourge RC, Naftel DC, Costanzo-Nordin MR, Kirklin JK, Young JB, Kubo SH, Olivari MT, Kasper EK. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. *J Heart Lung Transplant* 1993;12:549−562	244	221	10
92	Hillebrands JL, Klatter FA, van den Hurk BM, Popa ER, Nieuwenhuis P, Rozing J. Origin of neointimal endothelium and alpha-actin-positive smooth muscle cells in transplant arteriosclerosis. *J Clin Invest* 2001;107:1411−1422.	239	219	14
93	Dib N, Michler RE, Pagani FD, Wright S, Kereiakes DJ, Lengerich R, Binkley P, Buchele D, Anand I, Swingen C, Di Carli MF, Thomas JD, Jaber WA, Opie SR, Campbell A, McCarthy P, Yeager M, Dilsizian V, Griffith BP, Korn R, Kreuger SK, Ghazoul M, MacLellan WR, Fonarow G, Eisen HJ, Dinsmore J, Diethrich E. Safety and feasibility of autologous myoblast transplantation in patients with ischemic cardiomyopathy: four-year follow-up. *Circulation* 2005;112:1748−1755.	238	226	18
94	Dew MA, Kormos RL, Roth LH, Murali S, DiMartini A, Griffith BP. Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation. *J Heart Lung Transplant* 1999;18:549−562.	238	208	13
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96	Fang JC, Kinlay S, Beltrame J, Hikiti H, Wainstein M, Behrendt D, Suh J, Frei B, Mudge GH, Selwyn AP, Ganz P. Effect of vitamins C and E on progression of transplant-associated arteriosclerosis: a randomised trial. *Lancet* 2002;359:1108−1113.	232	214	15
97	Zheng H, Webber S, Zeevi A, Schuetz E, Zhang J, Bowman P, Boyle G, Law Y, Miller S, Lamba J, Burckart GJ. Tacrolimus dosing in pediatric heart transplant patients is related to CYP3A5 and MDR1 gene polymorphisms. *Am J Transplant* 2003;3:477−483.	232	228	15
98		230	209	11

(*continued*)

Table 1 (***Continued***)

Rank	Article	All citations	No self-citations	Citations-per-year*
	Girgis RE, Tu I, Berry GJ, Reichenspurner H, Valentine VG, Conte JV, Ting A, Johnstone I, Miller J, Robbins RC, Reitz BA, Theodore J. Risk factors for the development of obliterative bronchiolitis after lung transplantation. *J Heart Lung Transplant* 1996;15:1200−1208.			
199	Boucek MM, Mashburn C, Dunn SM, Frizell R, Edwards L, Pietra B, Campbell D, Denver Children's Pediatric Heart Transplant T. Pediatric heart transplantation after declaration of cardiocirculatory death. *N Engl J Med* 2008;359:709−714.	229	225	23
100	Lin SS, Weidner BC, Byrne GW, Diamond LE, Lawson JH, Hoopes CW, Daniels LJ, Daggett CW, Parker W, Harland RC, Davis RD, Bollinger RR, Logan JS, Platt JL. The role of antibodies in acute vascular rejection of pig-to-baboon cardiac transplants. *J Clin Invest* 1998;101:1745−1756.	227	155	11
Total citations		**40,660**	**37,450**	

* Rounded to the nearest whole number.

abstract, and keywords were: "heart transplant*" or "cardiac transplant*" or "myocardial transplant*" or "heart allograft*" or "cardiac allograft*" or "myocardial allograft*" or "heart graft*" or "cardiac graft*" or "myocardial graft*" or "heart lung transplant*" or "heart-lung transplant*" or "orthotopic heart transplant*" or "orthotopic cardiac transplant*."

The search was performed in the first week of February 2018 and yielded a total of 55,042 results. After filtering the search results by including only "journal articles" in the field of "medicine," the results were narrowed to 34,049 articles. We included only original research articles. Review articles, systematic reviews, meta-analyses, consensus reports and guidelines were excluded but registry data and transplantation reports were included. We calculated the citation-per-year value for all included articles and obtained the journals' impact factors from 2016 Journal Citation Reports (Clarivate Analytics, 2017). Regarding the origin of the articles, we used the first investigator's country to make such determination. Both animal and human studies were included, and no date or language restrictions were applied. The wildcard character (*) was used in appropriate positions as described above to account for spelling variations. The presence or absence of an abstract was not part of the inclusion criteria, and we included studies that were only reported as abstracts. Scopus has a "cited by" option which arranges articles in ascending or descending order based on number of times cited. The articles were arranged in descending manner from most cited to least cited, and both reviewers

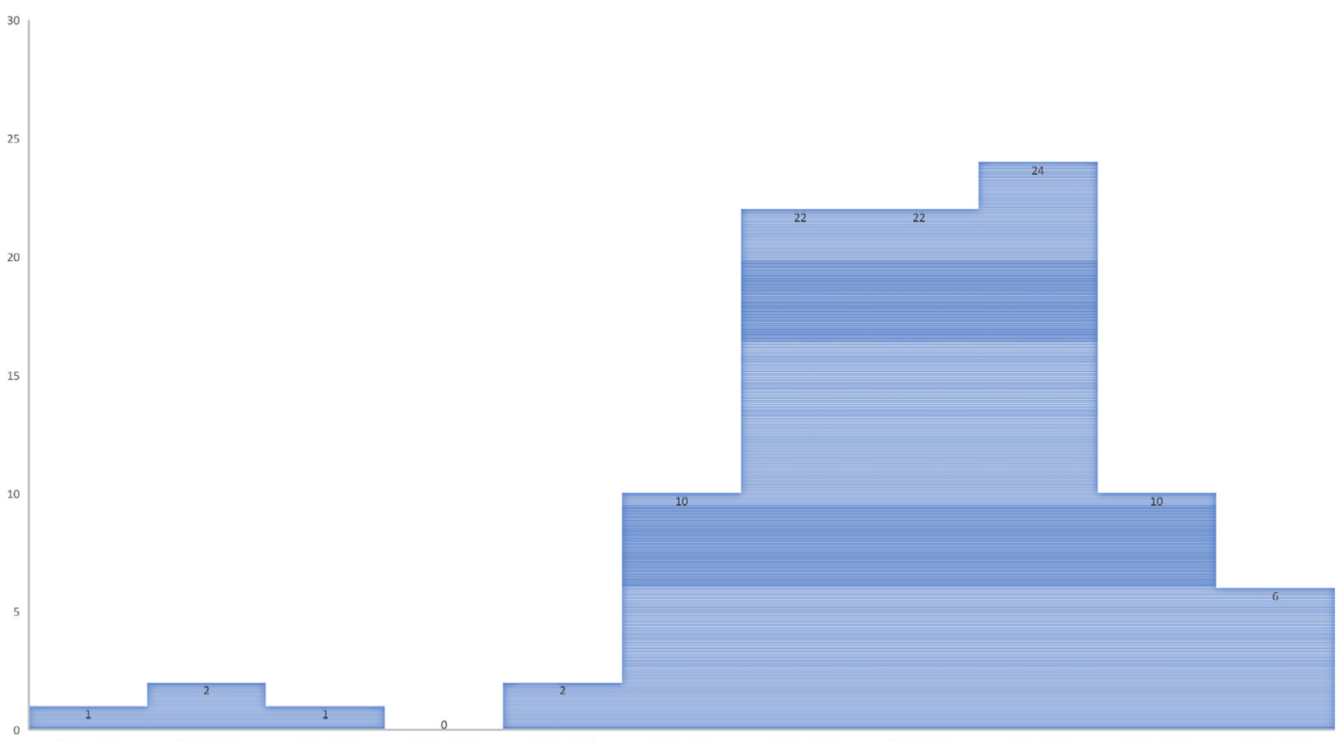

Figure 1. Top 100 articles cited in heart transplantation literature grouped in 5-year intervals.

Table 2
Journals arranged by total number of articles with respective impact factor and citation count.

Journal	Number of articles	Impact factor (2016)	Total number of citations
Journal of Heart and Lung Transplant	19	7.114	5586
Circulation	16	19.309	6584
New England Journal of Medicine	12	72.406	6957
Transplantation	10	3.678	3740
Journal of Experimental Medicine	7	11.91	2189
Journal of Clinical Investigation	4	12.784	1632
Journal of American College of Cardiology	4	19.896	1480
Journal of Thoracic and Cardiovascular Surgery	3	4.446	2098
Lancet	3	47.831	1298
Science	2	37.205	1112
Journal of Molecular and Cellular Cardiology	2	5.68	910
Nature Medicine	2	29.886	995
American Journal of Transplantation	2	6.165	545
Circulation Research	2	13.965	1007
JAMA: The Journal of American Medical Association	1	44.405	755
Journal of the American Academy of Dermatology	1	7.002	575
Kidney International	1	8.395	479
South African Medical Journal	1	0.566 (2001)	481
Surgical Forum	1	4.307	386
Annals of Thoracic Surgery	1	3.7	317
American Journal of Pathology	1	4.057	276
European Heart Journal	1	20.212	260
Journal of Infectious disease	1	6.273	254
Clinical Infectious disease	1	8.216	251
American Journal of Cardiology	1	3.398	250
Chest	1	6.147	248

independently assessed the list for inclusion. Both reviewers were blinded to each other's results throughout the literature review process; however, the final lists of the top 100 cited articles were then compared. There were minimal differences among the reviewers and discrepancies were resolved through discussion. The selected articles were scrutinized for data extraction. The list of articles was exported into Microsoft Excel 2016, which was used to create tables and figures.

For each article, we extracted the citation count (including and excluding self-citations), year of publication, journal, country of origin, number of investigators, gender of first/senior investigators, and funding type. Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were expressed as numbers and percentages (%). We performed the Pearson correlation coefficient test to assess the association between the journal's impact factor and the number of articles included in the list. The Mann-U Whitney test was used to assess the association between the presence or absence of funding with the number of citations, while the Kruskal-Wallis test was used to assess the association between the different types of funding and the number of citations. The Kendall's tau test was used to determine if there was a significant difference in the ranking of the articles after exclusion of self-citations. IBM SPSS Statistics version 23.0 (IBM Corporation, Armonk, New York) was used for all statistical analyses and a p-value < 0.05 was the criterion for significance.

Results

The top 100 cited articles relating to heart transplant, including total number of citations per article with and without exclusion of self-citations, as well as citations-per-year, are listed in Table 1. The top article was cited 1,376 times and the least was cited 227 times. The total number of citations for the entire list was 40,660, of which 3,210 (8.0%) were self-citations. These top 100 articles were published in 25 different journals between 1960 and 2013. Sixty-seven percent (n = 67) of the articles were related to human studies. The most productive 5-year time period was between 2000 and 2005, when 24 of the 100 publications were produced. The least productive 5-year time period was between 1975 and 1980 with zero of the articles published during that span (Figure 1). Of the 25 journals that published the top 100 articles, the Journal of Heart and Lung Transplantation (JHLT) had the most articles (n = 19), followed by Circulation (n = 16), and New England Journal of Medicine (NEJM) (n = 12). Although NEJM was only the third largest contributor in terms of number of published articles, its articles were the most frequently cited at 6,597 citations. Circulation was the second most frequently cited journal with 6,584 citations and JHLT was third with 5,586 citations (Table 2).

There was no correlation between the impact factor and the number of articles produced per journal (n = 25; r = 0.21, p = 0.30). Eighteen different countries produced the 100 articles, with the majority of articles (82%) originating from the U.S. (Figure 2). With regards to funding,

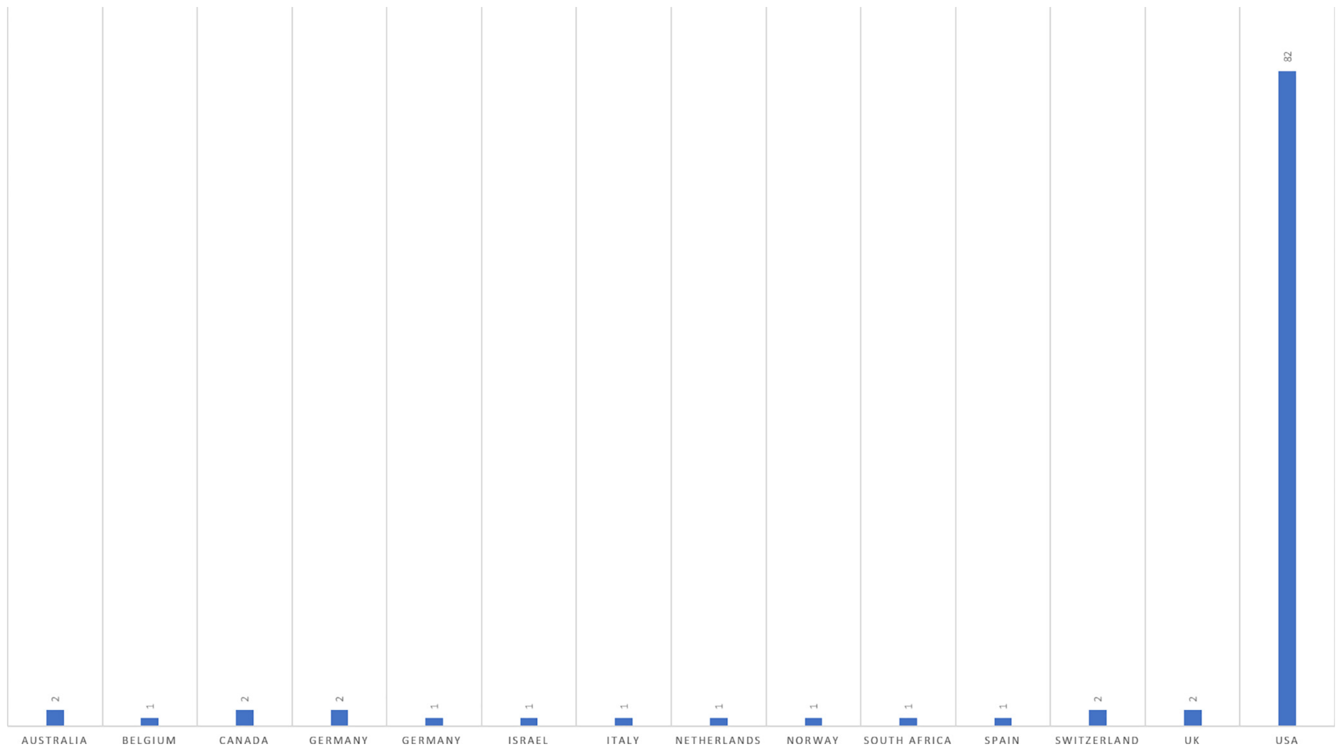

Figure 2. Top 100 articles cited in heart transplantation literature grouped by country of origin.

64% of the articles acknowledged some type of funding, out of which 16 were funded privately, 42 publicly, and 6 with both types of funding. The presence and type of funding were not associated with the number of citations ($p = 0.31$ and 0.13, respectively).

Though we imposed no language restriction, all of the top 100 articles were published in English. A total of 758 different investigators contributed to the 100 articles. The median number of investigators per report was 8 (IQR 6) with over 85% of the first and senior investigators being men (Figure 3). Seventeen of the 758 investigators had at least 5 articles in the list of top 100 articles (Table 3).

Discussion

This bibliometric analysis is the first of its kind on heart transplant literature, and it demonstrates several noteworthy findings. Firstly, the predominance of the most cited articles were human studies despite the pivotal role that animal studies had in paving the way for the development of the practice of cardiac surgery and heart transplantation in the modern era.[13] Secondly, there was a temporal variation across decades in terms of the most heavily cited publications. This was evidenced by the peak publication period occurring between 2000 and 2005 when nearly a quarter of the top 100 articles was produced, whereas there was a nadir seen between 1975 and 1980 when none of the top 100 cited articles were produced. Additionally, while the first human heart transplant occurred as early as 1964, and the first human-to-human heart transplant took place in 1967, the first publication among the top 100 was in 1960.[14] It is also notable that the vast majority of lead and senior investigators were men.

Ono and Lindsey published the most cited article on heart transplant to date.[13] In 1964, they described a new surgical technique of orthotopic heart transplant in rats, where they utilized an end-to-side anastomosis rather than end-to-end anastomosis resulting in the elimination of the previously encountered, serious complication of paraplegia in rat heart transplant recipients. This was a major breakthrough at the time, paving the way shortly thereafter with further modifications of surgical techniques leading to the realization of the dream of the first successful human-to-human heart transplant.

The year 1991 witnessed the publication of the second most cited article by Mancini et al.,[15] where they assessed the prognostic value of peak exercise oxygen consumption (Vo_2), significantly adding to the existing literature on optimizing the timing of heart transplantation for heart failure patients in the ambulatory setting. In their analysis, they found that peak Vo_2 was the best predictor of survival, among many other important variables, and that in patients with a peak Vo_2 greater than 14 ml/kg/min, it was shown to be generally safe to defer heart transplantation without a significant impact on patient mortality. This concept of delaying transplantation, if feasible, remains an important consideration given the scarcity of donor organs and the limited expected survival post-transplant, thus assisting with allocating available organs to those who would derive the most benefit and cannot afford a long wait. However, they also emphasized that their observed cut-off of a peak VO_2 of 14 ml/kg/min should not necessarily be adhered to in all patients, reminding us of the importance of considering many variables in combination when determining optimal timing of transplantation. More than 25 years later, this sentinel report and its findings continue to inform decision-making in nearly all transplant centers around the globe.

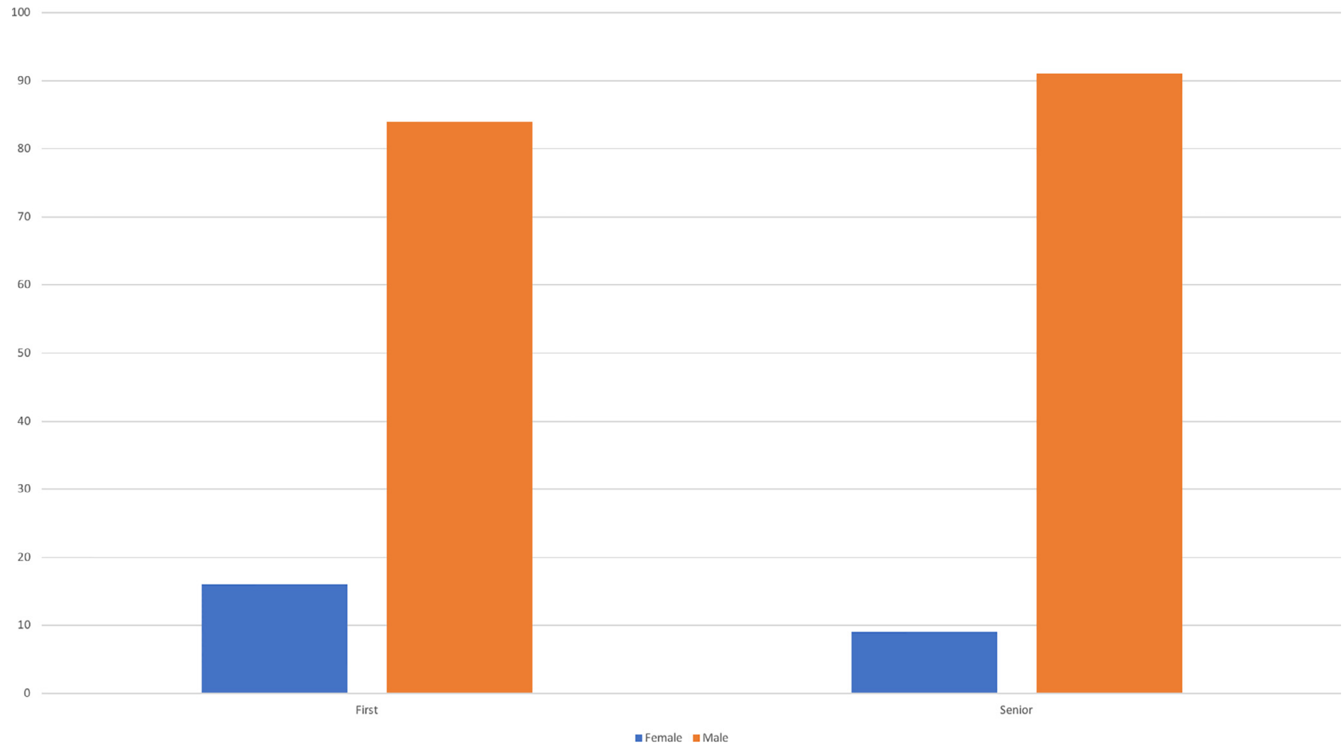

Figure 3. Gender distribution of first and senior authors.

Four years later, in 1995, Kobashigawa et al. published the third most cited article,[16] where they tested the effects of pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, on outcomes after heart transplantation. It was known at the time that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or "statins," have favorable effects in terms of reducing blood cholesterol levels, but there was speculation about possible beneficial immunosuppressive effects of statins that would be ideal in the heart transplant population. This clinical trial demonstrated that, in addition to the anticipated cholesterol-lowering effect, there was a reduction in the incidence of cardiac transplant rejection with hemodynamic compromise and a superior 1-year survival in the pravastatin group. Additionally, the pravastatin group showed lesser progression of coronary vasculopathy at 1 year. Incredibly, this study remains the only randomized clinical trial in heart transplantation to date to demonstrate a survival benefit of a particular therapy.

Bibliometric analysis is a useful tool to scrutinize the scientific literature and extract necessary information that may help to direct future research by informing scientists, funding bodies, and different stakeholders of the past, present, and potential future of a particular research area.[7,17] For instance, our analysis may provide scientists and researchers a general idea about the most influential articles in the field of heart transplantation, on which further work can be built upon or attempts on closing unfilled research gaps can be made. Our study also highlights the large output, not only in terms of citation frequency, but also the number of highly cited articles produced by those journals with high impact factors such as JHLT, Circulation, and NEJM in the present analysis. This, however, needs to be interpreted with caution, since other factors may contribute to a higher number of citations. One of these factors is time since publication, with a selective advantage for older articles which may be surpassed by other, more recent articles if allowed a comparable accrual of time passage. For that reason, we reported citations-per-year for each article to give a better estimate when the time factor is more or less eliminated. Despite this, overall, the impact factor did not have a strong or statistically significant correlation with the number of articles produced by each respective journal, but only with the citation frequency per report, as would be expected. Also, the self-citations phenomenon was present in our list, and it did have a significant effect on the final rank order; this imposes a bias in terms of solely relying on total number of citations to assess impact of articles. That being said, some reports suggest that funding agencies, such as the National Institutes of Health, should channel their funds toward the most influential researchers as assessed by citation count as a major criterion.[18] Although solely relying on citation frequency to assess the influence of an article or investigator remains a matter of debate, it remains among the factors that are considered for allocating funds.[19] Despite the mentioned reservations, our analysis provides relevant information in that regard.

The significant male predominance in first and senior investigator positions, with only about 15% female representation, highlights the major gender disparity that exists in terms of impactful heart transplant research output. Surgery, particularly cardiac surgery, remains a male-dominated field.[20] This finding in our study, though not surprising, continues to highlight important gender disparities that exist in the field of medicine and is an

Table 3
Authors with ≥ 5 articles in the top 100 articles.

Author	Articles	Author's current affiliation	H-index
Leah Bennett Edwards	9	United Network for Organ Sharing, Richmond, Virginia, United States	53
Jason D. M. Christie	8	University of Pennsylvania, Pulmonary and Critical Care Medicine, Philadelphia, United States	62
Fabienne Dobbels	8	KU Leuven, Department of Public Health and Primary Care, 3000 Leuven, Belgium	46
Axel O. Rahmel	8	Deutsche Stiftung Organ transplantation, Frankfurt am Main, Germany	40
Marshall I. Hertz	7	University of Minnesota Twin Cities, Critical Care and Sleep Medicine, Minneapolis,	61
Richard R. Kirk	7	UT Southwestern Medical Center, Dallas, United States	35
Anna Y. Kucheryavaya	7	International Society for Heart and Lung Transplantation Thoracic Transplant Registry, Dallas, United States	36
Donna M. Mancini	7	Columbia University Medical Center, Department of Medicine, New York, United States	79
Keith David Aaronson	6	University of Michigan Health System, Division of Cardiovascular Medicine, Ann Arbor, United States	49
Francis D. Pagani	6	University of Michigan Health System, Department of Cardiac Surgery, Ann Arbor, United States	60
Josef Stehlik	6	University of Utah Health Care, Salt Lake City, United States	42
Howard J. Eisen	6	Drexel University College of Medicine, Department of Medicine, Philadelphia, United States	40
Mark M. Boucek	5	Joe DiMaggio Children's Hospital, The Cardiac Center, Hollywood, United States	46
Anne I. Dipchand	5	Hospital for Sick Children University of Toronto, Department of Pediatrics, Toronto, Canada	37
Bartley Bartley Griffith	5	University of Maryland School of Medicine, Division of Cardiac Surgery, Baltimore, United States	82
Edward B. Stinson	5	Stanford University, Department of Cardiothoracic Surgery, Palo Alto, United States	80
David O. Taylor	5	Cleveland Clinic Foundation, Department of Cardiovascular Medicine, Cleveland, United States	51

endorsement for those who continue to promote and encourage an increased role of women in both clinical cardiovascular practice and research in cardiothoracic surgery.[20–23]

Despite its several strengths, our study is not free from limitations. For instance, Scopus has been reported to occasionally miss older citations occurring before 1980[24,25] and it entails a pragmatic restriction as a single database with a potential for English language bias. We also did not include textbooks as part of our search, which may impose omission bias. However, we deemed it more consistent with our bibliometric analysis to include only original research articles, hence our decision to also exclude review articles and meta-analyses. Additionally, we obtained official journal impact factors from the 2016 Journal Citation Reports (Clarivate Analytics, 2017). Nonetheless, since some of our captured articles are older studies, some impact factors were not available in recent years as in the case of South African Medical Journal, which was only available until 2001.[3] Another journal was called Surgical Forum,[14] for which there was no specific impact factor, since it has been merged or incorporated within the Journal of American College of Surgeons; hence we used the latter's impact factor for analysis purposes. Finally, we acknowledge that citation frequency should not be solely used to assess the true impact of an article and that the true value is in the content therein. However, citations remain a valuable tool and an accurate surrogate to the value of a particular study or discovery in a certain field as determined by the collective community of investigators who cite such reports.[26,27]

Our study highlights key features of the most highly cited scientific literature on heart transplant, with a list of the top 100 most impactful articles of our era, namely the first 50 years of heart transplantation. It also provides insight into trends of published work in the field and may serve as useful guidance to researchers and funding bodies on relevant prolific areas of research with hopes that the next 50 years become as fruitful and revolutionary as the first 50 that we currently celebrate.

Disclosures

The investigators have no conflicts of interest to disclose.

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