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META-ANALYSIS

Research priority setting in organ transplantation: a systematic review

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SUMMARY

Barriers to access and long-term complications remain a challenge in transplantation. Further advancements may be achieved through research priority setting with patient engagement to strengthen its relevance. We evaluated research priority setting in solid organ transplantation and described stakeholder priorities. Databases were searched to October 2016. We synthesized the findings descriptively. The 28 studies ($n = 2071$ participants) addressed kidney [9 (32%)], heart [7 (25%)], liver [3 (11%)], lung [1 (4%)], pancreas [1 (4%)], and nonspecified organ transplantation [7 (25%)] using consensus conferences, expert panel meetings, workshops, surveys, focus groups, interviews, and the Delphi technique. Nine (32%) reported patient involvement. The 336 research priorities addressed the following: organ donation [43 priorities (14 studies)]; waitlisting and allocation [43 (10 studies)]; histocompatibility and immunology [31 (8 studies)]; immunosuppression [21 (10 studies)]; graft-related complications [38 (13 studies)]; recipient (non-graft-related) complications [86 (14 studies)]; reproduction [14 (1 study)], psychosocial and lifestyle [49 (7 studies)]; and disparities in access and outcomes [10 (4 studies)]. The priorities identified were broad but only one-third of initiatives engaged patients/caregivers, and details of the process were lacking. Setting research priorities in an explicit manner with patient involvement can guide investment toward the shared priorities of patients and health professionals.

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Key words
complications, patient engagement, patient-centered care, research priority setting, transplantation

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Introduction

The considerable investment into research on solid organ transplantation has translated into marked improvements in short-term graft survival, but less so for longer term outcomes [1–4]. The 10-year graft survival remains at 50–70% after one year post-kidney transplant [5,6]. Death with a functioning graft due

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cardiovascular disease, infection, cancer, and diabetes [7–14], the debilitating side-effects of immunosuppression, and the severe shortage of transplantable organs [15,16] are some of the major hurdles to the overall success of transplantation. In view of these broad-ranging complexities and unresolved challenges in transplantation, progress may be achieved through strategic and transparent prioritization of research to strengthen the legitimacy, efficiency, and relevance of research [17–19].

Major organizations, including the World Health Organization [20], recognize research priority setting as essential for maximizing the impact of investments. Also, given the well-documented mismatches between patient and health professional priorities [21], there are now increasing efforts worldwide to involve patients in priority setting to ensure the research agenda includes questions of patient relevance [17,21–23]. This may in turn promote the uptake and implementation of research evidence. Yet, in the context of solid organ transplantation, research priority setting initiatives appear intermittent and variable, and the extent and impact of patient/caregiver engagement is uncertain [24].

This study aimed to evaluate existing research priority setting projects in solid organ transplantation and to describe the priorities of stakeholders. A detailed scan of research priority setting may inform ways to improve stakeholder engagement that is inclusive of transplant patients, caregivers, and their healthcare providers, in an explicit process to identify high-priority research. This may ultimately increase the value and contribution of research to the field of solid organ transplantation, and achieve the long-awaited outcomes hoped for in transplant patients.

Methods

Selection criteria

Studies that directly elicited and identified research priorities for adult solid organ transplantation from stakeholders (including patients, healthcare providers, policymakers, and researchers), and published in any language in peer-reviewed journals were eligible. Methods of identifying priorities could include (but not limited to) surveys, qualitative studies, consensus methods (Delphi survey, nominal group technique), and workshops. Studies assessing priorities for practice and policy (quality indicators); nonresearch articles (policy documents, clinical guidelines, editorials, commentaries); reports of a conference, workshop or meeting that did not include information about the participants and methods; and basic science research, epidemiological studies, guidelines, and economic evaluations were excluded.

Data sources and searches

The search strategy comprised Medical Subject Headings (MeSH) terms and text words for solid organ transplantation and text words for research priorities and research agenda (Appendix S1: SDC Materials and Methods [25]). The searches were conducted in MEDLINE, Embase, and PsycINFO from database inception to October 31, 2016. We also searched the James Lind Alliance website [26] and Google Scholar. CH/AT screened the titles and abstracts and removed those that did not meet the inclusion criteria. The full texts of the remaining studies were assessed, and those that were ineligible were excluded.

Appraisal

There is no universally accepted or standardized checklist for appraising research priority setting in health. We adapted existing frameworks and principles of good practice in research priority setting [27–29], to develop a comprehensive 32-item checklist to assess the reporting and transparency of reporting research priority setting (Appendix S1: SDC Materials and Methods). This checklist covers nine domains: context and scope; governance and team; inclusion of stakeholders/participants; identification and collection of research topics/questions; prioritization of research topics/questions; output; evaluation and feedback; dissemination and translation; and funding and conflict of interest. Two reviewers (CH/BS) independently assessed each study. Any disagreements were resolved through discussion with a third reviewer (AT).

Synthesis

We conducted a descriptive synthesis to categorize the research priorities on organ transplantation identified in the included studies. The full text of each article was entered into HYPERRESEARCH (ResearchWare, INC 2009, version 3.0.3, Randolph, MA, USA) software for managing and coding textual data. BS/CH/AT independently identified and coded the research topics selected as priorities reported in each paper. Similar topics were grouped and classified into broader research categories.

The research priorities were mapped to the type of solid organ transplant (heart, kidney, liver, lung, multiple organs, or not specified).

Results

Literature search and study characteristics

We identified and included 28 eligible studies, that involved 2071 participants [patients/caregivers/living kidney donors ($n = 631$), and health professionals ($n = 1025$)] (Fig. 1). Three studies did not report the number of participants within each stakeholder group separately, and four studies did not report the total number of participants. The study characteristics are provided in Table 1. Priority setting was conducted in the area of kidney (9 studies), heart (7 studies), liver (3 studies), lung (1 study), and pancreas (1 study) transplantation, and seven studies covered organ transplantation broadly (i.e., non-organ-specific). Eighteen (64%) studies addressed a specific scope in terms of discipline (e.g., nursing, social science), complication (e.g., primary graft dysfunction, antibody-mediated rejection, infection), or population (e.g., older adults, sensitized recipients), while 10 (36%) addressed the type of organ transplantation more broadly.

Nine (32%) studies reported patient/caregiver involvement, but this was limited to kidney and heart transplantation. The methods for identifying research priorities included: online and postal surveys [8 (29%) studies], focus groups [3 (11%) studies], telephone and face-to-face interviews [2 (8%) studies], multiround Delphi surveys [1 (4%) study], online forums [1 (4%) study], and other group-based meetings [including consensus conferences (11 studies), working group discussions (9 studies), workshops (8 studies), and symposiums (2 studies)]. Sixteen (57%) used a combination of these methods. The studies were conducted in the United States, Canada, the United Kingdom, Australia and the Netherlands, and 15 were multinational studies.

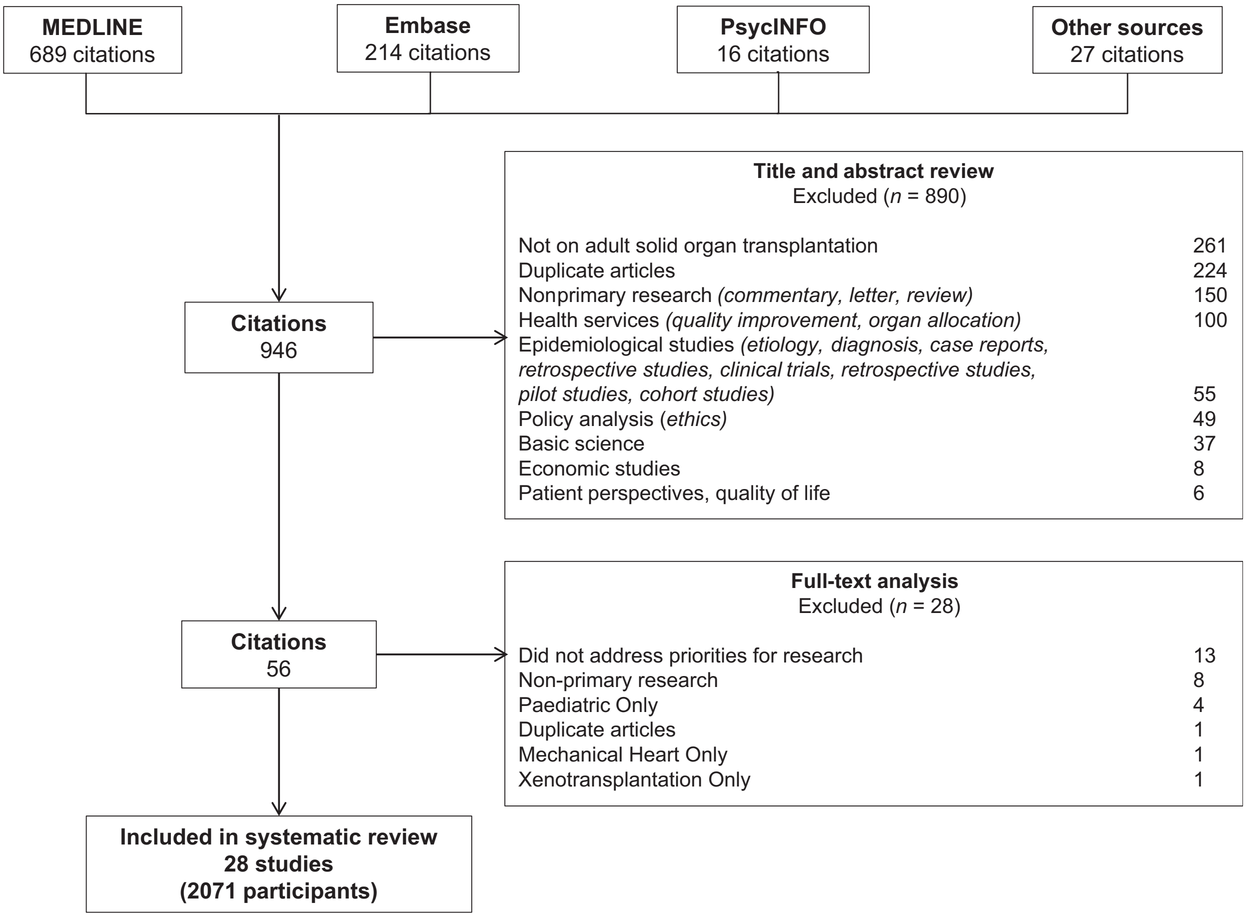

Figure 1 Search results.

Table 1. Characteristics of the included studies (28 studies).

Study ID	Country	Total *n*	Stakeholders (*n*)*							Outline of methods*	Focus/scope
			Patients	Living donors	Caregivers	Physicians	Allied Health, nurses, others	Policymakers	Researchers		
Heart											
Cotts 2014 [44]	Canada, US	196	✓			43	14			Survey 1 during symposium (*n* = 57), community meetings, online forums, online survey (*n* = 139)	Adult congenital heart disease
Goosens 2012 [61]	International	37					32		5	Two-round Delphi survey (37), semistructured telephone interviews (6 survey participants)	Adult congenital heart disease nursing
Kobashigawa 2014 [32]	International	71				71				Online surveys (*n* = 47), breakout sessions, consensus conference	Primary graft dysfunction
Kobashigawa 2011 [49]	International	83				83				Surveys (*n* = 46), breakout sessions, consensus conference	Antibody-mediated rejection
Kobashigawa 2009 [48]	International	71				71				Surveys (*n* = 23), breakout sessions, consensus conference	Sensitized recipients
Manolio 1992 [45]	US	NS								Workshop	Idiopathic dilated cardiomyopathy
Shah 2012 [38]	US	22				19	1		2	Working group	Heart transplantation and evidence-based outcomes

Table 1. Continued.

Study ID	Country	Total *n*	Stakeholders (*n*)*							Outline of methods*	Focus/scope
			Patients	Living donors	Caregivers	Physicians	Allied Health, nurses, others	Policymakers	Researchers		
Kidney											
ASN 2005 [36]	US, Canada	20				17			3	Retreats, working groups	Nephrology (including kidney transplantation)
Knight 2016 [43]	UK	459	151	72	15	150	31		16	JLA—Initial survey ($n = 183$); prioritization survey ($n = 256$); workshop ($n = 20$)	Kidney transplantation
LaPointe Rudow 2015 [33]	US, Canada	142	✓		✓	✓	✓	✓	✓	Literature review, polling (20 transplant programs), surveys, teleconferences, workgroups, consensus conference	Living kidney donation
Manns 2014 [34]	Canada	351	184		42	33	92			Conference calls with steering group ($n = 11$), review of guidelines, online and postal survey ($n = 317$), interim voting (steering group), workshop with NGT and group exercises ($n = 34$), consensus	Management of kidney failure
Melcher 2013 [35]	US, Canada	73	✓		✓	✓	✓	✓	✓	Teleconference, workgroups, consensus conference	Kidney paired donation

Table 1. Continued.

Study ID	Country	Total *n*	Stakeholders (*n*)* Patients	Living donors	Caregivers	Physicians	Allied Health, nurses, others	Policymakers	Researchers	Outline of methods*	Focus/scope
Schipper 2011 [54]	Netherlands	74	74							Individual interviews (*n* = 20), focus groups (*n* = 54)	Coping, family and mastery (social science)
Sharif 2014 [55]	International	24				✓			✓	Consensus meetings	Post-transplant diabetes mellitus
Tong 2015 [39]	Australia	58	23		7	16	8		4	Workshop, ranking exercise	Chronic kidney disease (including kidney transplantation)
Tong 2008 [40]	Australia	63	63							Focus groups	Chronic kidney disease (including kidney transplantation)
Liver											
Durand 2008 [31]	International	NS				✓			✓	Consensus conference, working groups	Expanded criteria donors
NIH 1983 [37]	US	33				28	3		2	Consensus conference	Liver transplantation
Wiesner 2003 [41]	International	35				✓				Consensus conference	Hepatitis C
Lung											
Larson 2005 [56]	US	NS				✓	✓		✓	Literature review, workshop, committee meetings by conference call and consultations	Respiratory nursing
Pancreas											
Bartlett 2016 [42]	International	33				✓			✓	Workshop	Pancreas transplantation

Table 1. Continued.

Study ID	Country	Total *n*	Stakeholders (*n*)* Patients	Living donors	Caregivers	Physicians	Allied Health, nurses, others	Policymakers	Researchers	Outline of methods*	Focus/scope
Non-organ-specific											
Abecassis 2012 [30]	US	NS				✓			✓	Workshop	Transplantation in older adults
Caserta 2014 [52]	US	50+				✓			✓	Workshop	Roseoloviruses
Fine 2009 [50]	International	66				✓	✓		✓	Breakout groups, conference calls, consensus conference	Nonadherence
Higgins 2006 [47]	International	38				28	3		7	Symposium	Disparities in ethnic minorities
Mathur 2014 [46]	Canada, US	60	✓			✓		✓	✓	Conference, survey	Exercise
McKay 2005 [51]	US	12				11			1	Conference, focus groups	Reproduction/ pregnancy
Preiksaitis 2005 [53]	Canada	NS				✓			✓	Working group	Cytomegalovirus

ASN, American Society of Nephrology; JLA, James Lind Alliance; NGT, nominal group technique; NS, not stated; UK, United Kingdom; US, United States.

*, Number of participants reported only if specified in the study; ✓ indicates the stakeholder group was involved, but numbers were not specified, and some numbers may not add up total n if numbers were not specified for each stakeholder group.

Appraisal of reporting

The studies reported on 6–28 of the 32 items assessed (Table 2). All studies described the scope in terms of the health condition, the target audience and end users of the research, the study type (e.g., clinical trials), and methods for prioritizing or achieving consensus on research topics. Twenty two (79%) studies described the characteristics of the stakeholders involved in priority setting, 21 (75%) detailed methods for collecting the research topics/questions, and 17 (61%) outlined the strategy or action plan for implementing the priorities. No studies described how the process of priority setting was evaluated, only three (4%) indicated that stakeholder feedback was obtained and integrated into the proposed research priorities.

Synthesis

We identified 336 research priorities which were synthesized into ten broad areas: organ donation [43 (14 studies)]; waitlisting and allocation [43 (10 studies)]; histocompatibility and immunology [31 (8 studies)]; immunosuppression [21 (10 studies)]; graft-related complications [38 (13 studies)]; recipient (non-graft-related) complications [86 (14 studies)]; reproduction [14 (1 study)], psychosocial and lifestyle [49 (7 studies)]; and disparities in access and outcomes [10 (4 studies)]. Across the studies, the priorities ranged in scope and were presented as statements, topics and/or questions with varying details provided in terms of the population, intervention, comparator, and outcomes.

The priorities for each of these topics (and their respective subtopics) are described in the following section. Figure 2 shows the number of studies that identified the priorities for each type of organ transplant.

Organ donation

Fourteen (50%) studies identified research priorities for organ donation [30–43], which were primarily focused on the procurement and preservation of deceased donor organs; increasing deceased and living donation rates; support for living donors; and surgical technique. Assessing the suitability of individual organs for transplantation in a reliable way was suggested in a kidney transplantation priority setting exercise [43]. One study included the development of "bioengineered organs" [43] as a research priority.

Deceased donation

Eight (29%) studies identified priorities on improving organ procurement and preservation processes [30–32,35,37,38,41–43]. Minimizing ischemia–reperfusion injury was specifically prioritized [30,38,41,42] including evaluating the impact of different preservation fluids on graft survival [31,32,37,43], optimizing *ex vivo* transport devices [32,37,43], and determining ways to reduce resources (i.e., time, cost) required for transport of kidneys between transplant centers in paired-kidney exchange programs [35]. Determining the best strategy to maximize the availability of kidneys [34,39,40], such as improving family consent in deceased donation and "taking different cultural groups into account" [39], and optimizing the use of "marginal" [30] organs were suggested.

Living donation

Improving educational, social, and psychological support and assessing health risks among living donors were identified as priorities in seven (25%) studies [30,33,35,39–41,43]. Stakeholders prioritized research to improve consistency in the information provided to donors by physicians and transplant programs [33,35], and to improve the efficiency of the donation process [33]. Eight (29%) studies prioritized research to improve living donation rates [30,33–35,38–40,43], with specific suggestions including "peer mentorship programs to increase KPD [kidney paired donation]" [35], removal of financial barriers [33], improving awareness about nondirect donor programs [35], and extending criteria for elderly donor–recipient pairs [39]. Research on surgical techniques for nephrectomy [32] and peri-operative care [30] on living kidney donor outcomes such as end-stage kidney disease and mortality [33,43], and safety considerations for older donors [30] were prioritized.

Waitlisting and organ allocation

Ten (36%) studies identified research priorities on waitlisting and organ allocation [30,31,34,37,38,41,43–46].

Acceptance and management of wait-listed patients

Research to improve timing, "access and the selection process for transplantation" [34], as well as pretransplant education for patients [43], was prioritized [30,31,34,37,38,43,44]. Suggestions to "evaluate exercise

Table 2. Appraisal of comprehensiveness of reporting (total number of studies = 28).

ID	Reporting item	References	Total studies *n* (%)
A	**Context and scope**		
1	Define geographical scope (e.g., global, national, area health services)	[31–49,51,53–55,61]	24 (86)
2	Define health area or focus (e.g., disease)	[30–56,61]	28 (100)
3	Define end users of research (e.g., patients)	[30–56,61]	28 (100)
4	Define the target audience (e.g., funders, researchers)	[30–56,61]	28 (100)
5	Identify the research focus (e.g., clinical, basic science, health services)	[30–56,61]	28 (100)
6	Identify the type of research question (e.g., diagnosis, prevention, intervention)	[30–53,55,56,61]	27 (96)
7	Define the time frame (e.g., short- or long-term priorities)	[36,38,55]	3 (11)
B	**Governance and team**		
8	Describe selection of the project leader/s and team (e.g., Steering Committee, working group)	[30,33–36,38,39,43–45,51,56]	12 (43)
9	Describe the characteristics of the project leader/team members (e.g., stakeholder group, organizations represented)	[30,31,33–36,38,39,41,43–47,50–52,54,56]	19 (68)
10	Training or expertise in research priority setting	[34,39,43]	3 (11)
C	**Inclusion of stakeholders/participants**		
11	Define the inclusion criteria for stakeholder groups involved in the priority setting exercise	[32–34,39–41,43,44,46,51,54,61]	12 (43)
12	State the strategy or method for identifying and engaging stakeholders (e.g., hospital, social media)	[33–35,39,40,43,44,54,55,61]	10 (36)
13	Indicate the number of participants and/or organizations involved	[30,32–37,39–52,54,55,61]	24 (86)
14	Describe the characteristics of stakeholders	[32–41,43,44,46–52,54,55,61,62]	22 (79)
15	Reimbursement for participation	[39,40,54]	4 (14)
D	**Identification and collection of research topics/questions**		
16	Describe methods for collecting all research topics or questions (e.g., systematic reviews, focus groups, workshops, surveys)	[32–35,39–46,48–51,53–56,61,62]	20 (74)
17	Describe method for collating and/or categorizing topics or questions (e.g., framework, taxonomy used to aggregate topics)	[33–35,39–41,43,44,50,51,54,61]	12 (43)
18	Describe methods or reason for initial removal of topics or questions (e.g., duplication, scope)	[33,34,39,43,44,50]	6 (21)
19	Describe methods for refining research questions/topics	[33–35,39–41,43,44,46,50,54,56,61]	13 (46)
20	Cross-check to identify if research questions have been answered	[32–37,39–41,43–52,54–56,61]	23 (82)
21	Describe number of research questions/topics at each stage of the process	[30,32–37,39–41,43–50,52–56,61]	24 (86)
E	**Prioritization of research topics/questions**		
22	Describe methods for prioritizing or achieving consensus on priority or achieving consensus on priority research areas, topics, or questions (e.g., Delphi technique, nominal group technique, workshops, ranking scores)	[30–56,61]	28 (100)
23	Provide reasons for excluding research topics/questions	[34,39,43,44,61]	5 (18)
F	**Output**		
24	Define specificity of research priorities (e.g., area, topic, questions, themes)	[30,32–36,39–47,49–56,61]	24 (86)

Table 2. Continued.

ID	Reporting item	References	Total studies *n* (%)
G	**Evaluation and feedback**		
25	Describe how the research priorities exercise was evaluated (e.g., surveys, interviews, debriefing sessions)	–	0 (0)
26	Describe how priorities were made accessible for review by stakeholders (e.g., report)	[33,35,39,40,51,61]	7 (25)
27	State how feedback was integrated	[35,51,61]	3 (11)
H	**Dissemination, translation, and implementation**		
28	Outline the strategy or action plans for implementing priorities	[30,31,33,35–39,41,43,45–48,50,53,56]	17 (61)
29	Describe how impact will be measured	[35,38,39,46,53]	5 (18)
I	**Funding and conflict of interest**		
30	State sources of funding	[30,32–40,42–44,46,48,49,52–55]	20 (71)
31	Outline the budget and/or cost	[39]	1 (4)
32	Provide declaration of conflict of interest	[30,32–35,38–40,42–44,46,48,54–56]	16 (57)

capacity, function, and frailty" [46], "cognition, health literacy, and medication adherence" [30], and to understand the rationale for cardiovascular and cancer screening in older transplant candidates [30] were put forward as potential ways to inform the selection and monitoring of transplant candidates. One priority setting exercise in kidney transplantation specifically included factors "such as age, body mass index, history of cancer, co-morbidities" [43] for determining patient suitability for transplantation.

Expanded criteria or high-risk organs

Five (18%) studies identified priorities about expanded criteria or high-risk organs [30,31,38,45]. Research to determine the threshold for accepting expanded criteria donors for transplantation [31], to improve acceptance of older donors (for heart transplantation) [38], and determining ways to best match donors and recipients (e.g., use of "marginal donors in elderly recipients" [38], "illness-based allocation" [30], and age-matching [30,43], nephron dosing [43]), were suggested to optimize efficient use of a scare resource [30,31,38,45].

Histocompatibility and immunology

Eight (29%) studies identified priorities relating to histocompatibility and immunology [30,36,38,42,43,47–49]. Understanding the genetics of immune response and "pharmacogenetic" profiles [36,47], and immune system function in terms of "immune exhaustion," "enhanced alloreactivity," or "innate and cellular response" were suggested [30,36,38,47]. In heart transplantation, two studies focused on the management of sensitized patients and proposed treatments to detect, suppress or remove HLA antibodies [48,49]. In kidney transplantation, "how can we prevent sensitization in patients with a failing transplant" [43] and "does routine screening for and treatment of donor-specific antibodies improve outcomes?" [43] and "improving transplant rates in highly-sensitized patients" were identified as high-priority research questions [43]. Also, studies on tolerance (e.g., T-regulatory cells, induction of hemooxygenase 1), and reduction of antibody levels in blood group incompatible transplants were identified as priorities [43].

Immunosuppression therapy

Ten (36%) studies identified research priorities on immunosuppression, with most focused on maintenance therapy [30,37–43,47,50]. Optimizing and individualizing

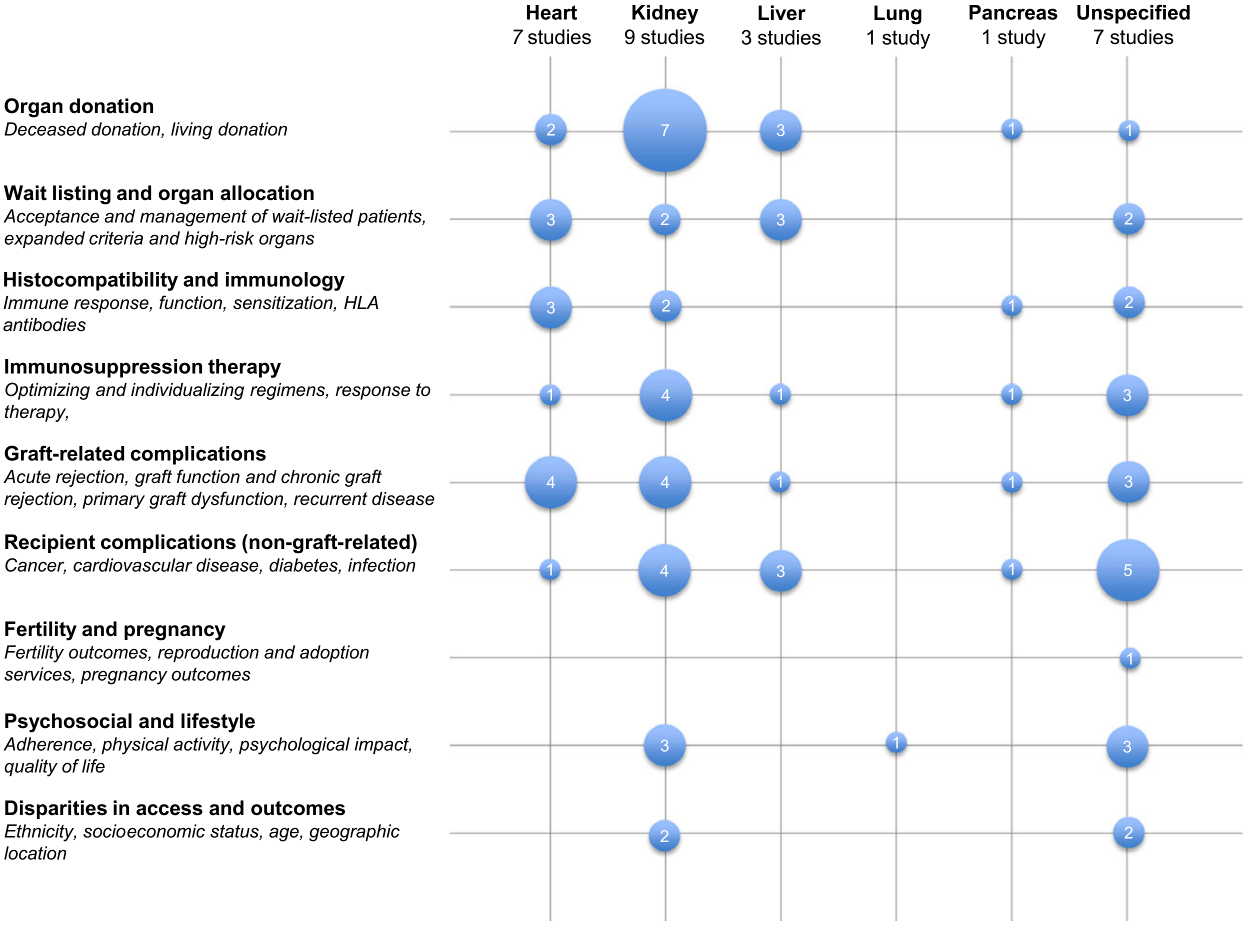

Figure 2 Matrix of priority research topics identified for solid organ transplantation. *Size (and number indicated) of the circles corresponds to the number of studies that identified the topic as a research priority.

regimens to improve outcomes [38–41,43]; identifying the "best combination of immunosuppressive drugs" [43]; improving strategies for monitoring the level of immunosuppression [43]; developing ways to assess response to therapy [30,38,50] including "surrogate marker(s) for adequacy of immunosuppression" [50], understanding the pharmacokinetics in older transplant recipients [30]; and strategies to "wean" off or eliminate the need for immunosuppression were suggested [38,40]. In pancreas transplantation, "clinical trials of non-nephrotoxic immunosuppression [42]" was identified as a research priority.

Graft-related complications

Thirteen (46%) studies identified research priorities for graft-related complications including acute rejection, graft function and chronic rejection, and primary graft dysfunction [30,32,36–43,48,49,51]. One study in kidney transplantation identified the prevention of disease recurrence (glomerulonephritis) post-transplant as a priority [43].

Acute rejection

Research priorities relating to acute rejection were specified in eight studies [30,36–38,41,43,48,49]. A "histological, serological, and clinical" [38] understanding of antibody-mediated rejection (AMR), identifying biomarkers to help diagnose and predict AMR [38], optimizing treatment with intravenous immunoglobulin, corticosteroids, plasmapheresis or antiproliferative agents (including in combination) [30,38,41,43,48,49], and the assessing impact of AMR on outcomes [36] were prioritized.

Graft function and chronic graft rejection

Nine studies identified both graft function and chronic graft rejection as priorities [30,36,38–43,51]. Studies that involved patients emphasized the need to improve graft survival [39,40,43]. Three studies specified developing surrogate biomarkers to predict long-term graft outcomes [30,38] and identifying other risk factors (molecular and pathological) of graft damage [36]. Research to “characterize newer forms of rejection” was suggested [38]. In liver transplantation, health professionals suggested that research was needed to assess the “relationship between the degrees of fibrosis and immunosuppression” [41]. Stakeholders in a pancreas transplantation workshop suggested “developing validated measures of pancreatic organ function” [42].

Primary graft dysfunction

One study in cardiac transplantation outlined the need to identify “biomarkers,” “inflammatory cascade,” and role of “iron deficiency anemia” associated with primary graft dysfunction (PGD), and treatment of PGD [32].

Prevention and management of recipient complications (non-graft-related)

Fourteen (50%) studies reported research priorities to prevent mortality and manage other non-graft-related complications (including cancer, cardiovascular disease, diabetes, and infection) in transplant recipients [30,31,36–38,41–43,46,51–55]. Some broad research priorities including minimizing side-effects (e.g., diarrhea [43]) and organ damage were proposed [30]. The impact of pancreas transplantation on kidney function was proposed [42].

Cancer

Identifying the risk factors for cancer [38], improving strategies for cancer screening [30], minimizing the risk of cancer [43], and the determining the “rates of malignancy” [55] were proposed as research priorities. In liver transplantation, understanding the risk of hepatocellular carcinoma and post-transplant malignancy, as well as the prevention of recurrence and treatment of hepatocellular cancer were prioritized for research among health professionals [30,31,37].

Cardiovascular disease

Research to determine how “immunosuppression influences the development or progression of coronary artery disease” [30] was identified as a priority. In kidney transplantation, understanding the “role of inflammatory mediators in the development of cardiovascular disease” [36] and the relationship between cardiovascular disease and chronic kidney disease [36] were proposed [36,55]. The “impact of intensive risk marker modification on major adverse cardiac allograft events” and managing “coronary allograft vasculopathy” were specifically noted [38]. Two studies identified a need for research to address hypertension and hyperlipidemia [38,46].

Diabetes

Pharmacological and nonpharmacological (exercise, lifestyle modification) interventions [46,55] to prevent, delay, and treat diabetes were prioritized. The “risk versus benefit analysis” of post-transplant diabetes mellitus versus graft outcomes (i.e., rejection) was also identified as a priority [55]. Participants also emphasized the need for research on glucose control and the association between “fasting/postprandial glucose and HbA1c” with mortality, graft and patient outcomes [38,55].

Infection

Eight studies identified research priorities on the diagnosis, prevention and management of infections [30,31,37,41,43,51–53], which were mainly focused on viral infections (CMV [30,52,53], EBV [30], HCV [37,41,51]). Prevention of CMV through prophylactic therapy [41,53], determining “residual risk of late-onset CMV disease” [53], and linking “viral load determinations with prediction of disease” [53] were specified. In liver transplantation, participants prioritized the effect of specific immunosuppressive regimens, interferon, and donor–recipient HLA matching on recurrence of HCV [37,41], “longitudinal histological studies” in patients with recurrent HCV [41] to examine outcomes such as cirrhosis, and “maternal–fetal” HCV transmission [51]. One study identified priorities on roseoloviruses and ciHHV-6 [52].

Fertility and pregnancy

One study specifically elicited research priorities on fertility and pregnancy in transplantation [51]. Fertility outcomes in transplant recipients, assisted reproduction and adoption services, and timing of pregnancy based on graft function were specified as priorities [51]. Pregnancy in kidney transplant recipients encompassed research topics on monitoring, in utero exposure to immunosuppression, risk of graft and CVD complications, optimal immunosuppression, and breast-feeding [51].

Psychosocial and lifestyle

Seven (25%) studies identified psychosocial and lifestyle aspects of transplantation as research priorities [30,39,40,46,50,54,56].

Adherence

Research to define nonadherence, assess the economic cost and clinical outcomes of nonadherence, determine the cost-effectiveness of interventions to improve adherence, and to evaluate impact of the "healthcare system, healthcare team, and healthcare providers on the incidence and outcome of non-adherence" were identified as priorities [50]. A pharmacy clinic was suggested in a priority setting workshop that involved health professionals and patients [39].

Physical activity

Physical activity and exercise (e.g., circuit, resistance, high-intensity training, supervised program, pedometer-based walking) were identified as a priority research area in three studies [30,46,54]. Topics included exercise interventions (including a focus on safety considerations in elderly recipients [30,46]) to prevent graft and other health complications and hospitalization, and to improve cognition and quality of life [46] in transplant candidates and recipients.

Psychological impact

All three studies that identified psychological impact in donors, transplant recipients and family members as a research priority involved patients [39,40,54]. Research priorities included assessing psychological outcomes, ascertaining patient concerns, and evaluating psychological interventions.

Quality of life

Three studies addressed priorities pertaining to quality of life [30,46,56]. Improving self-management and quality of life were proposed [46,56], with one study focused on quality of life in elderly transplant recipients [30].

Disparities in access and outcomes

Four (14%) studies reported research priorities to address disparities in access and outcomes in deceased organ donation and living kidney donation [30,33,43,47], generally in terms of ethnicity, income, age, and geographical location [30,33,43,47]. One study on living kidney donation proposed that "shift in care practices could reduce or eliminate such disparities" [33]. A UK study in kidney transplantation suggested research to "ensure fair and equal access to transplantation across the UK" [43]. In the context of post-kidney transplantation, improving outcomes particularly in "adolescent and young adult kidney transplant recipients" [43] was noted as a research priority.

Discussion

The priorities for research in solid organ transplantation spanned a diverse range of topics, with the most frequently identified focused on increasing deceased and living donation, and the prevention and management of long-term graft and clinical complications (namely cancer, cardiovascular disease, diabetes, and infection) in transplant recipients. Stakeholders also identified research priorities in the areas of waitlisting and organ allocation, histocompatibility and immunology, optimizing immunosuppressive regimens, fertility and pregnancy, psychosocial and lifestyle impact, and disparities in access and outcomes in solid organ transplantation. However, patient/caregivers were only involved in one-third of research priority setting activities. No studies in liver, lung and pancreas transplantation involved patients. Also, the processes used to establish these priorities often lacked detail with less than half of the studies reporting details on the stakeholder inclusion criteria, method for collating and categorizing research topics, reasons for removing topics or questions, methods for refining research questions, evaluation of the priority setting process, and how stakeholder feedback was obtain and integrated in the final set of priorities.

Most of the research priorities were identified in the context of kidney (9 studies), heart (7 studies), followed by liver transplantation (3 studies). Lung and pancreas transplantation comprised the focus of one study each. Seven studies did not focus on a specific type of organ transplantation. In kidney transplantation, there was considerable focus on organ donation, which encompassed improving living kidney donation in terms of donation rates and donor outcomes. For heart transplantation, the research priorities clustered around prevention and management of graft-related complications including primary graft dysfunction, organ allocation, and histocompatibility and immunology. Research priority setting in liver transplantation largely covered organ donation and allocation, and also specific recipient complications such as HCV and liver fibrosis. Lung transplantation was addressed specifically in only one study, which identified nursing research priorities related to recipient quality of life [56]. Research priorities identified in a recent opinion leaders meeting for pancreas transplantation focused on mortality and secondary complications (including kidney function), validating measures for pancreatic function, organ preservation, use of nonnephrotoxic immunosuppression, and identifying the risk of recurrent disease [42].

Some differences between the priorities of patients/caregivers and health professionals were identified in the 32% of studies reported patient involvement [33–35,39,40,43,44,46,54]. Of the seven studies that also included both patients and health professionals [33–35,39,44,46], only three studies, which addressed kidney transplantation, made direct comparisons of priorities between both stakeholder groups [34,39,43]. In the Canadian priority setting initiative, “improving access to donor kidneys and transplantation, and how transplantation work up could be more efficient” [34] was submitted mostly by health professionals compared with patients. In the other priority setting workshop conducted in chronic kidney disease in Australia, patients/caregivers prioritized “what strategies will improve donor family consent to deceased donation taking different cultural groups into account” as their top research priority, and ranked “reducing side-effects of immunosuppressive therapy” higher than health professionals [39]. In the UK kidney transplantation priority setting study, patients gave higher priority to questions relating to immunosuppression (including side-effects), organ preservation, and equity of access; living kidney donors prioritized organ suitability and promotion of living kidney donors, and health professionals focused more on patient assessment for transplantation, suitability of organs, and antibody-mediated rejection [43]. It was noted that some questions in the top ten were suggested by more patients than health professionals, for example, “long-term impacts of donor nephrectomy” [43].

Overall, it was apparent that studies involving patients/caregivers identified research priorities relating to improving organ donation, patient and family education and support, graft survival, reducing side-effects of medications, and quality of life. In contrast, the more technical or policy aspects of transplantation such as allocation and use of extended criteria or high-risk organs, HLA antibodies and sensitization, biological risk factors of graft complications and clinical outcomes, and the pharmacokinetics of immunosuppression, appear to only arise in priority setting exercises conducted among health professionals.

This systematic review provides a comprehensive overview of research priorities in solid organ transplantation derived from priority setting initiatives that involved a range of stakeholders. However, there are some limitations. Most of the studies were conducted in high-income English-speaking countries. Six studies were published more than a decade ago, and the relevance of the research priorities identified in older studies may be questionable. We also acknowledge that mapping these research priorities to funded research is difficult and beyond the scope of this review. Also, given the limited stakeholder involvement (particularly of patients/caregivers) and reporting of the methods, there is some uncertainty about the extent to which the research priorities identified reflect the priorities of the broader community.

Overall, patient involvement and details about the process for establishing the research priorities were lacking. Most studies (57%) used standalone group-based approaches (working group discussion, consensus conferences, symposiums, workshops), which were often convened for a specific problem or population (e.g., expanded criteria donors, HCV, transplantation in older population). For future research priority setting initiatives, we suggest a partnership, systematic, and transparent approach. The James Lind Alliance has developed a multistep priority setting process, which facilitates extensive engagement with multiple stakeholders, including patients. A Steering Group is initially convened involving patients, clinicians, other relevant stakeholders, and a member with expertise in research priority setting partnerships. The methods proposed by the JLA includes the identification and invitation of potential partners at both an organizational and individual level; initial stakeholder meetings to build awareness; identification of research questions; refinement of research questions; interim prioritization through discussion, surveys, or consultations processes; and final prioritization through consensus, which is typically achieved in facilitated face-to-face workshops. However, other methods such as Delphi technique, nominal group technique, and online forums may be useful [27]. These provide stakeholders the opportunity to identify, refine, distill, and validate research priorities. The JLA approach has been successfully used in over 30 other areas, with recent examples in liver disease, autism, bipolar disorders, osteoarthritis, eating disorders, and cancer” [26] and involves surveys and facilitated workshops opportunity to identify, refine, distill, and validate research priorities [27]. This approach was also used (or adapted) in three priority setting exercises in organ transplantation [34,39,43].

We suggest that it would be important to evaluate research priority setting partnerships in terms of stakeholder satisfaction, endorsement by health-sector organizations, impact on the research agenda, and changes in resource allocation of funding agencies [28]. For example, the research priorities identified in priority setting partnerships for multiple sclerosis, autism, childhood disability, and palliative and end-of-life care have impacted research funding decisions with government and major philanthropic agencies directing funding toward prioritized areas [57,58]. The results from the Multiple Sclerosis Society's JLA PSP results directly informed their research strategies and research grant submissions to the society must include information about how the research addresses the priorities identified [59]. In 2016, the UK Marie Curie Charity providing support for patients with terminal illness allocated more than $1.7 million USD to funding applications that addressed research priorities identified by the Palliative and end of life care Priority Setting Partnership (PeolcPSP) [60]. We also recommend subsequent work to evaluate patient engagement in priority setting in the context of other stages in research including study design, conduct, dissemination, implementation, and evaluation of impact [58].

The research priorities identified in solid organ transplantation are broad in scope and appear to signal the major challenges faced by the transplant community. However, it is unclear whether they explicitly align with the concerns and values of transplant recipients who to date have had marginal involvement in establishing research priorities. Also the prioritization processes are often ambiguous and this can raise questions about the legitimacy of decisions, particularly about investing limited resources available to toward high-priority research. Setting research priorities in an explicit manner with equitable involvement of patients can help to ensure that resources are directed toward research that is important and relevant to patients and health professionals in solid organ transplantation.

Authorship

AT: designed the study, collected and analyzed the data and drafted the manuscript. BS and CH: participated in the research design, collected and analyzed the data and contributed to writing of the manuscript. JRC, PM, NS, SC, CSH, SH, AS and JCC: contributed to the design of the study, participated in data analysis and reviewed the manuscript for important intellectual content.

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Conflicts of interest

The authors have no conflict of interest to declare.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. SDC Materials and Methods: search strategies and appraisal framework.

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