Clinical Decision Support Systems Used in Transplantation: Are They Tools for Success or an Unnecessary Gadget? A Systematic Review

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Abstract. Although clinical decision support systems (CDSSs) have been used since the 1970s for a wide variety of clinical tasks including optimization of medication orders, improved documentation, and improved patient adherence, to date, no systematic reviews have been carried out to assess their utilization and efficacy in transplant medicine. The aim of this study is to systematically review studies that utilized a CDSS and assess impact on patient outcomes. A total of 48 articles were identified as meeting the author-derived inclusion criteria, including tools for posttransplant monitoring, pretransplant risk assessment, waiting list management, immunosuppressant management, and interpretation of histopathology. Studies included 15 984 transplant recipients. Tools aimed at helping with transplant patient immunosuppressant management were the most common (19 studies). Thirty-four studies (85%) found an overall clinical benefit following the implementation of a CDSS in clinical practice. Although there are limitations to the existing literature, current evidence suggests that implementing CDSS in transplant clinical settings may improve outcomes for patients. Limited evidence was found using more advanced technologies such as artificial intelligence in transplantation, and future studies should investigate the role of these emerging technologies.

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INTRODUCTION

Computer-based clinical decision support systems (CDSSs) have been used in medicine since the 1970s. However, these early programs were often only used in academic settings and not integrated into routine clinical practice. Evolution from paper medical records into integrated electronic health records (EHRs) has opened the possibility of greater use of automated technologies to guide patient care in everyday medicine.

CDSS can be defined as tools to improve outcomes in healthcare by helping end users (healthcare professionals, patients, family members) make decisions with the assistance of clinical knowledge, patient information, or other health-related information.[1] Most CDSS use software designed to assist in decision-making with the inputs comprised of patient characteristics, laboratory and other test results, and other clinical information, which are then matched to a computer-based knowledge repository. The

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recommendations for patient care are generated and displayed, with the final decision on clinical care being made by the clinician.[2]

CDSS can be classified depending on the key components used in their decision-making processes either into knowledge-based or non–knowledge-based. CDSS that fall into a knowledge-based system rely on a repository of rules and then check against those rules/knowledge and make a decision that is materialized as an output or action.[3] The underlying rules are defined in the CDSS, usually drawing on knowledge from clinical practice guidelines, consensus statements, or the medical literature. Non–knowledge-based CDSS relies on computing through statistical pattern recognition. Some of the techniques used within non–knowledge-based CDSS tools include statistical methods, which achieve results by the creation of problem-specific probability models. Another non–knowledge-based tool, machine learning (ML), varies from statistical techniques by concentrating on predictions based on "learning" algorithms to find patterns in data and are often considered flexible models.[4] Deep learning (DL) is another branch of ML that is being utilized in some newer CDSS tools. DL is unique as it enables the discovery of complex structure in big data sets using models that are made up of multiple layers of algorithms that data pass through to form a neural network, which is inspired by the neural pathways in the human brain.[5,6]

ML models find patterns using previously collected, rich patient data (eg, registry data, EHR data) and are used to predict outcomes for new cases while making minimal assumptions regarding the systems from which the data were generated. This information can aid clinical decision-making. These models are especially helpful in the presence of nonlinear, complex relationships.[4] Such tools have been used extensively in specialties such as radiology (eg, image recognition) but have seen limited real-world use in other areas of medicine.[7] Reasons for this hesitancy to adopt such technologies may relate to uncertainty about the accuracy and generalizability of the underlying models or due to a lack of established clinical and ethical acceptability criteria around AI metrics. Another key factor in adopting the technology may lie in the transparency (explainability) of the models (the "black-box" phenomenon), where many of the more advanced ML techniques present predictions or recommendations without the clinician understanding how the decision was reached by the underlying model.[8] This challenge may be further amplified in transplantation where the high-stakes nature of a transplant decision makes the explainability and transparency of CDSS even more resonant.

Transplant medicine has a number of features that potentially lend well to the use of CDSS to assist in clinical practice. As a specialty, we have a wealth of data available for donor and recipient demographics and outcomes from national and international registries to assist in the development of non–knowledge-based systems. We also have robust, evidence-based national and international guidelines to allow the development of knowledge-based systems. Decision-making around suitability for transplantation, organ offer decisions, and posttransplant management is often complex, leading to a great deal of between-clinician and between-center variability in practice.

Despite several systematic review studies focused on CDSS within medicine and subsets of medicine including prescribing, no systematic reviews have been carried out to assesses their efficacy in transplant medicine.[9-11] Furthermore, a number of reviews question the usefulness of CDSS in the clinical setting and highlight the lack of vigorous testing of such tools and the perceived lack of usefulness of some tools by their end users.[12,13] The aim of this study is to perform a systematic review of studies that utilized a CDSS in clinical practice within transplant medicine and determine if it improved clinical outcomes including posttransplant monitoring, graft survival prediction, waiting list management, immunosuppressant management, and interpretation of histopathology.

MATERIALS AND METHODS

Literature Search Strategy

Original research articles on CDSSs utilized in clinical practice within transplant medicine were identified using the following databases: MEDLINE, AMED, CINAHL, EMBASE, PubMed, NCBI-PMC, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Transplant Library from inception to March 1, 2022 (full search strategy in **Search Strategy S1, SDC**, http://links.lww.com/TP/C756). No date or language limitations were applied. Clinicaltrials.gov was searched to identify ongoing studies.

A review of the reference lists of studies obtained from the search strategy were utilized to identify additional studies for inclusion. Researchers utilized the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist to include appropriate studies within this review. The study was registered on the PROSPERO database (CRD42022302463).

Selection Criteria

Inclusion criteria define research articles in which the CDSS technology was computerized and implemented prospectively in a clinical setting (those studies that reviewed the CDSS as an academic exercise were excluded). Studies were limited to solid organ transplantation including the liver, lung, heart, kidney, small bowel, and pancreas. Both pediatric and adult patients were included. In instances of overlapping study groups, if different clinical endpoints or uses for the CDSS were being analyzed, then all data were included. Types of study design included within this review were meta-analysis (of randomized control trials [RCTs]), RCTs, and prospective cohort studies. A data extraction sheet was created to identify CDSS design (eg, web-based, computer-based) and CDSS type, study clinical endpoints, and bias ratings (via checklists). The extraction and reference screening was conducted by two independent researchers (L.R.W. and A.S.), and any discrepancies were reviewed by the senior author (S.K.).

Risk of Bias Assessment

Depending on the study type, either the ROBINS-I tool (Risk Of Bias In Nonrandomized Studies of Interventions) or the ROB-2 tool (Risk of Bias 2) were used to identify risk of bias in the identified studies by two independent reviewers (L.R.W. and A.S.), with discrepancies being resolved by the senior author (S.K.). These assess risk of bias in the categories of confounding of the effect, study participants, outcome data, and reported results.[14,15]

Data Synthesis

Given the heterogeneity of interventions and outcome measures, and the design, and quality of the identified literature, a narrative synthesis is presented.

RESULTS

Included Studies

Of the initial 5176 studies that were identified via the search terms as detailed here, 15 were excluded as duplicates. Of those remaining, 4321 records were excluded on the basis of title and abstract. On full-text review, a further 503 were excluded as they were not used in clinical care or were a theoretical design, and 147 were excluded as they were not computer-based (instead relying on paper questionnaires or phone calls). A further 90 articles were excluded as they were not used in a decision-making process by a patient, medical team, or organization, and a final 69 articles were excluded for other reasons. The final screening process resulted in 48 articles for inclusion within this review (Figure 1).[16-63] CDSS identified fell into 5 categories: posttransplant monitoring (n = 21), graft survival prediction risk assessment (n = 4), waiting list management (n = 2), immunosuppressant management (n = 19), and

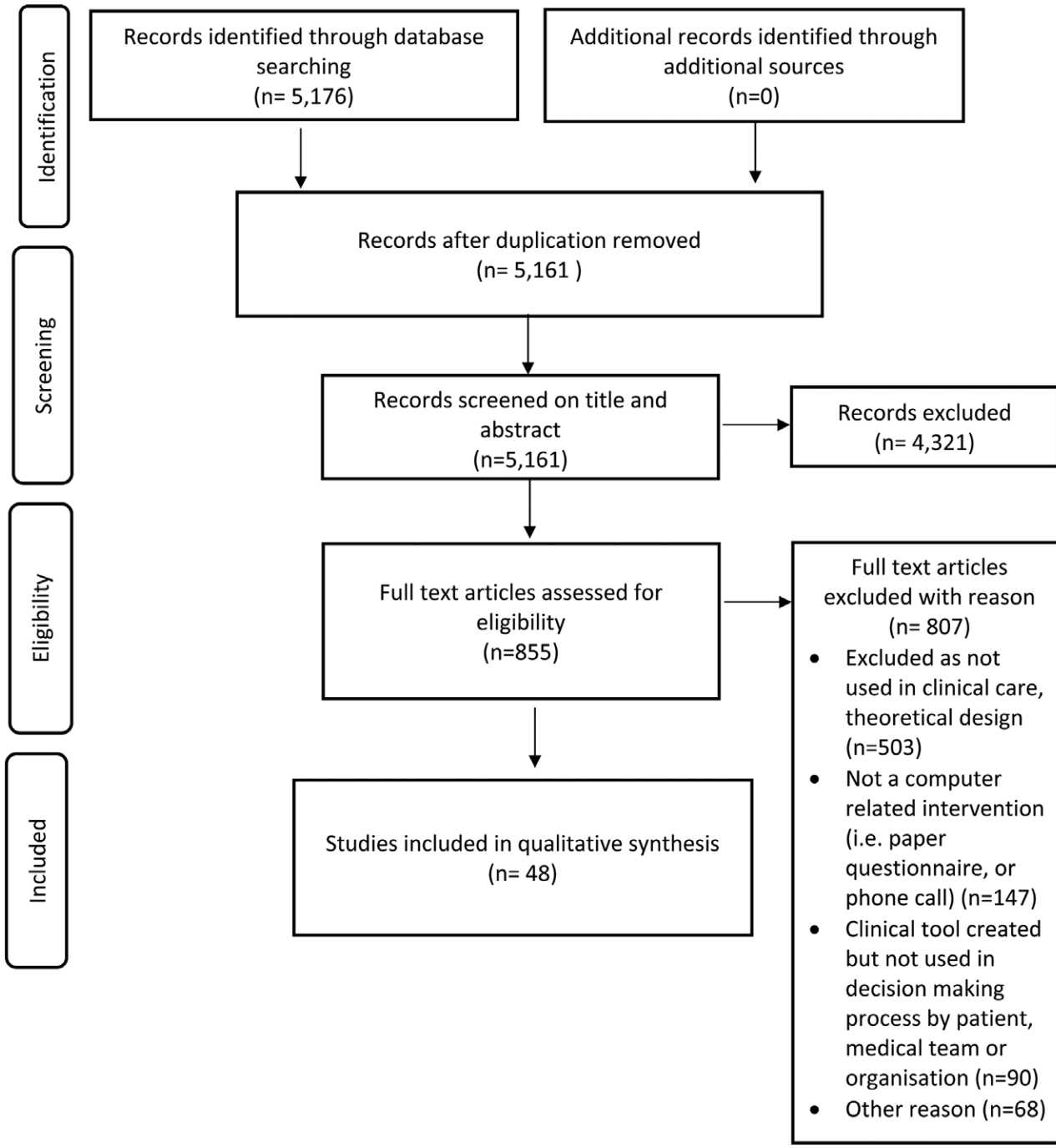

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of systematic identification, screening, eligibility, and inclusion criteria.

interpretation of histopathology (n = 2) (Tables 1–5, CDSS categories).

Risk of Bias Assessment

Risk of bias assessment for the included studies is provided in **Tables S1 and S2, SDC**, http://links.lww.com/TP/C756. Of the 26 cohort studies that were reviewed using the ROBIN-I checklist, more than half (n = 16, 61.5%) had a moderate risk of overall bias. Additionally, 15 studies had a potential risk of bias or no information provided about whether the outcome measures could have been influenced by knowledge of the intervention received as part of the trial. Similarly, of the 22 RCT studies evaluated using the ROB-2 checklist, the majority of the studies (n = 16, 72.7%) had some or high concerns regarding the overall risk of bias. Finally, reviewing the largest category of CDSS tool, posttransplant monitoring, more than half of the studies (n = 13, 59%) had moderate to high levels of concerns of overall bias.

Participants

Included studies reported outcomes from 15 984 transplant participants. The median number of participants within the included studies was 80.5 (range, 7–6129) with CDSSs used in graft survival prediction assessment having the largest participant cohort. For example, Loupy et al[58] assessed their posttransplant survival prediction tool in 4000 kidney recipients in 4 French centers and used a further 2129 kidney recipients as a validation cohort from 3 centers in Europe and 1428 from 3 centers in North America. There was a wide range of countries represented within the studies (Tables 1–5). Additionally, larger national registry data were used to create the ML models within CDSSs including the United Network for Organ Sharing (UNOS) as seen in the research by Cheng et al.[56] The majority of the CDSSs (n = 19) were designed for kidney transplant recipients. There were a number of CDSSs that were of a more generic nature and targeted multiple organ recipients such as the pancreas and kidney or lung, heart, and kidney (n = 7).[24,25,32,33,46,48,55]

Immunosuppressant Management

General Overview

Immunosuppressant management was the most common clinical outcome for CDSS tools included within this review (n = 26). This group of tools included more specific monitoring applications such as medication adherence posttransplant, dose adjustment, and highlighting potential drug interactions (Table 3: Results Summary).

User Interface

The most common user interface design of these tools was as a smartphone application (n = 12), potentially allowing quicker access for patients and clinicians using it when taking or prescribing medications, respectively. Seven studies implemented the CDSS to work in conjunction with a device such as an electronic pill box to monitor patient adherence or in one study, an ingestible device to monitor adherence and absorption of medication. Although all CDSS were implemented in clinical care in a clinical trial setting (ie, in a single center), several noted it would be challenging to implement it in widespread clinical practice due to patient intolerance of using an electronic pill container, where researchers described the device requiring the user having to move the pills from one container to another or feeling that the system was invasive.

CDSS Type

The vast majority of the tools focused on immunosuppressant management relied on a non–knowledge-based approach (n = 18). These non–knowledge-based approaches to back-end design were usually composed of simplistic logging systems of information that was then sent in real time (or slightly delayed transfer if clinicians collected the information once daily in the morning, for instance). An examples of non–knowledge-based back-end designs were employed by research groups such as Dobbles, Foster, Hardstaff, Henriksson, Jung, Levine, Melilli, Reese, and Zanetti-Yabur, where simple adherence information (date, time, medication amount) was registered by the patient and fed back to the medical team. Only 6 of the CDSS tools utilized non–knowledge-based approaches including Bayesian methods and other ML approaches to guide medication dosing. Tang et al and Tecen-Yucel et al both utilized other ML techniques within their CDSS tools, with Tang et al using a number of ML algorithms on a cohort of >1000 renal transplant patients to determine best practice tacrolimus dosing when compared with traditional dosing methods. Tecen-Yucel et al were able to identify drug–dose interactions in 80 renal transplant patients.[53,54]

Clinical Endpoints

Outcome measures used in CDSSs aimed to improve immunosuppressant management were extremely variable making them difficult to compare. However, almost all studies within this category examined medication adherence in some way. Some studies specifically approach adherence in terms of overall adherence to the number of pills ingested every day relative to the number of pills prescribed (Taking Adherence),[20] while other groups looked at more long-term medication adherence outcomes in comparison with usual care, such as Geramita et al. Finally, 6 studies compared the accuracy of the CDSS in comparison with experienced clinicians (or a standard drug calculation), and of these, all groups showed an improved clinical benefit with the use of a CDSS when compared with standard clinical care or intervention.[31,32,36,45,52,53] For instance, Åsberg et al found that their CDSS outperformed experienced transplant clinicians in prescribing cyclosporin A for renal transplant patients. Their CDSS tool provided a deviation from the predefined therapeutic window that was significantly lower compared with the control group (experienced clinicians) ($P = 0.042$).[31]

Posttransplant Monitoring

General Overview

Seven studies used CDSSs that facilitated posttransplant monitoring (Table 1). An additional seven CDSSs were previously mentioned under the "Immunosuppressant Management" category here as these tools had both posttransplant monitoring and immunosuppressant management features. Within the tools that facilitated posttransplant monitoring, many focused on patient empowerment following transplant through easy-to-use, handheld

TABLE 1.

Posttransplant monitoring

Paper details		Study design												
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall improvement?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
DeVito Dabbs et al[17]	2009	RCT	University of Pittsburgh Medical Center, USA, one center	Lung	Not mentioned	To determine the effects of Pocket PATH compared to standard care during the first 2 mo following discharge after lung transplantation	30	2 mo	Mobile app-based	Nonknowledge	Patient improvement	Yes	Yes	Qualitative	Yes
DeVito Dabbs et al[18]	2016	RCT	University of Pittsburgh Medical Center, USA (single center)	Lung	January 2009–December 2012; followed through December 2013	The impact of mHealth intervention on Lung transplant recipients to perform self-management behaviors	201	12 mo	Mobile app-based	Nonknowledge	Patient/family improvement and system improvement (messaging system between patient and transplant team)	Yes	Yes	Qualitative	Partially
Dew et al[16]	2004	Prospective cohort	University of Pittsburgh Medical Center, USA (single center)	Heart	Not stated	An evaluation of an internet-based psychosocial intervention for heart recipients and their families	60	4–6 mo	Web-based	Nonknowledge	Patient/family improvement	No	Yes	Qualitative	Partially
Duarte-Rojo et al[19]	2021	Prospective cohort	Starzl Transplantation Institute, Pittsburgh Liver Research Center, Pittsburgh, PA, USA, single center	Liver	July and December 2019	To determine the feasibility of liver transplant candidates using the EL-FIT app	28	4–8 wks after study enrollment	Mobile app-based	Nonknowledge	Patient improvement	Yes	No	Qualitative, quantitative	Yes

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TABLE 1. (Continued)

Paper details		Study design													
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall improvement?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Finkelstein et al[21]	2013	RCT	The University of Minnesota Medical Center lung transplant program, USA (single center)	Lung	October 2006 to April 2009	To determine the relative performance of a computer-based Bayesian algorithm compared with a manual nurse decision process for triaging clinical intervention in lung transplant recipients	65	2 y	Computer-based + home spirometry	Bayesian methods	Patient and system improvement/ economic to reduce cost of nurse-led follow-up	No	Yes	Qualitative, quantitative	No
Fleming et al[38]	2021	Parallel, 2-arm, semiblind, 1:1 RCT	Medical University of South Carolina, Charleston, SC, USA	Kidney	12 mo	To assess the efficacy of a pharmacist-led, mHealth-based intervention on improving medication safety and health outcomes compared to usual care.	136	12 mo	Mobile app-based	Nonknowledge	Medication safety and health outcomes	Yes	Yes	Qualitative, quantitative	Yes

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TABLE 1. (Continued)

Paper details		Study design													
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall improvement?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Garthwaite et al[38]	2004	Prospective cohort	St. James's University Hospital, Leeds, UK (single center)	Kidney	November 2000–2002, data were examined at 3-mo intervals for 2 y	To examine the effect of a computerized system that prompted the doctor with respect to cholesterol management in the routine adult renal transplant follow-up clinic	451	2-y period (data collected every 3 mo)	Computer-based	Knowledge-based	Clinical outcome—to increase number of post-renal patients on statins with high cholesterol and therefore, lower cholesterol levels in this patient population. System improvement - create an easier system to prompt clinicians to prescribe statins	Yes	No	Quantitative	Yes
Gomis-Pastor et al[39]	2020	Prospective cohort	Heart Failure and Heart Transplant Unit, Cardiology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Catalonia, Spain (single center)	Heart	July 15, 2016, to December 1, 2016	To validate mHeart to measure medication nonadherence in early stage HTxR in the home setting	31	1 mo	Mobile app-based	Nonknowledge	Patient/system improvement	Yes	No	Qualitative	NI

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TABLE 1. (Continued)

Paper details		Study design													
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall improvement?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Gonzales et al[40]	2021	RCT	Medical University of South Carolina; single center	Kidney	Between October 2017 and January 2019	To examine the efficacy of improving medication safety through a pharmacist-led, mobile health–based intervention	136	NI	Mobile app based	Nonknowledge	Patient improvement	Yes	Yes	Quantitative	Yes
Han et al[41]	2019	Prospective randomized controlled	Seoul National University Hospital, Seoul, Korea (single center)	Renal	November 2013 and May 2015	To evaluate whether the use of the Adhere4U mobile medication manager application could improve adherence among renal transplant recipients ≥1-y posttransplantation	138	180 d	Mobile app-based	Nonknowledge	Patient/system improvement	No	Yes	Qualitative, quantitative	No
Hardstaff et al[42]	2003	RCT	Freeman Hospital, Newcastle-upon-Tyne, UK	Kidney	Not stated	Assess the impact of feedback and time on self-medication practice	75	12 mo	Computer-based + electronic pill box	Nonknowledge	System/patient improvement	No	Yes	Quantitative	NI
Jiang et al[23]	2016	Cross-sectional correlational study	Acute cardiothoracic unit of the University of Pittsburgh Medical Center, USA	lung	December 2008 to December 2012	To examine the degree to which lung transplant patients followed decision support messages to report recorded critical values	96	1 y post-transplant	Mobile app-based	Nonknowledge	System improvement	Yes	No	Qualitative, quantitative	Partially

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TABLE 1. (Continued)

Paper details		Study design												
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall improvement?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Lerret et al[24]	2021	RCT	Pediatric heart, kidney, and liver transplant recipient family members from four major pediatric transplant centers in the United States	Heart, kidney, liver	October 2018 and March 2020	The first aim was to determine the feasibility of family member use of the intervention (myFAMI)	46	30 d	Mobile app-based	Nonknowledge	Patient/family improvement	No	Yes	Qualitative, quantitative	No
Melilli et al[48]	2021	Prospective, observational, multicenter, pilot study	Two different transplant centers in Barcelona, Spain (Bellvitge University Hospital and Hospital Clinic)	Kidney and liver	July to October 2018	2-phase trial in kidney and liver transplant recipients, investigating the degree of engagement to TrackYourMed, to track immunosuppression adherence	90	1 y (broken into 2 phases of 6 mo each)	Mobile app-based	Nonknowledge	Patient improvement/system improvement	Yes	No	Qualitative, quantitative	Yes
Morlion et al[25]	2002	Prospective cohort	Chest Service, Erasme University Hospital, Brussels, Belgium (single center)	bilateral-lung and heart–lung transplant	June 1998 and September 2000	To determine the sensitivity and positive predictive value of such monitoring for the detection of acute complications affecting the allograft	22	Median of 473 d (range, 60–822)	Web-based + home spirometry	Nonknowledge	Patient/system improvement	No	No	Qualitative, quantitative	No

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TABLE 1. (Continued)

Paper details		Study design													
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall improvement?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Sengpiel et al[26]	2010	RCT	Single university center	Lung	July 2007 to November 2008	To compare adherence to home spirometry	56	6 mo after discharge	Mobile app-based + home spirometry	Nonknowledge	Time efficiency in patient treatment	No	Yes	Qualitative, quantitative	No
Staes et al[51]	2008	Prospective Cohort	LDS Hospital, Salt Lake City, USA, single center	Liver	August 2003 and March 2005	To compare traditional result reporting-related clinical processes and timeliness of clinician responses after implementing computerized alerts	336	Approximately 1.5 y	Computer-based	Knowledge-based	System improvement	Yes	Yes	Qualitative, quantitative	Yes
Stine et al[27]	2020	Prospective cohort	Consecutive liver transplantation candidates, evaluated at the University of Virginia Charles O. Strickler Transplant Center outpatient clinic, USA (single center)	Liver	July 1, 2016, to September 30, 2016	To determine the feasibility of administration of the Patient-Reported Outcomes Measurement Information System (PROMIS-CAT) in liver transplant candidates electronically (iPad)	109	3 mo	Mobile app-based	Nonknowledge	Patient/system	No	No	Qualitative, quantitative	Partially

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TABLE 1. (Continued)

Paper details		Study design													
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall improvement?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Wagner et al[30]	1999	Prospective cohort	Cardiovascular Institute, University of Dresden, Dresden, Germany (one center)	X	December 1997	Test whether telemetric monitoring of graft function in lung transplant recipients allows reliable early diagnosis and treatment of infection or rejection	7	12 mo	Computer-based + home spirometry	Nonknowledge	Treatment improvement	Yes	Yes	Quantitative	NI
Wang et al[29]	2013	Prospective cohort study	Lung Transplant Home Monitoring Program (LTHMP) at the University of Minnesota, one center	Lung		To develop, implement, and test an automated decision system to provide early detection of clinically important bronchopulmonary events	58	60 d	Computer-based + home spirometry	Knowledge-based	System improvement	Yes	No	Quantitative	Yes
Watford et al[28]	2021	Prospective cohort	Division of Nephrology, Department of Medicine, Stanford University Medical Center, one center	Kidney	October 2017 to December 2018	To directly compare SF-36 PF to objectively obtained physical performance tests in a cohort of kidney transplant candidates approaching the top of the waitlist	199	1 y	Mobile app-based	Nonknowledge	Patient improvement	Yes	No	Qualitative, quantitative	Yes

CDSS, Clinical Decision Support System; HTxR, heart transplant; NI, no information; SF-36 PF, Short Form-36 physical function questionnaire.

TABLE 2.

Graft survival prediction

Paper details		Study design													
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall improvements? (Y/N)**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Aubert et al[59]	2021	Randomized trial	Multicenter study including 186 centers in 42 countries worldwide	Kidney	December 2013 to January 2016	Study the efficacy of iBox as a surrogate endpoint in an RCT and individual patient long-term kidney allograft survival from 1 to 11 y after randomization.	2037	1 y	Computer-based	Regression	Patient improvement	Yes	No	Quantitative	NI
Lenain et al[61]	2021	Prospective cohort study	2 European transplantation centers	Kidney	Lille transplantation center (January 1, 2007, and December 31, 2017); Leuven transplantation center (January 1, 2005, and January 31, 2013)	To externally validate the dynamic prediction of patient and kidney graft survival.	1637	5 y	Web-based	Modified Cox model	System validation	Yes	No	Quantitative	Yes
Loupy et al[58]	2019	Prospective cohort study	Four French centers, 3 centers in Europe, 3 centers in North America	Kidney	2002 and 2014	Develop a post-transplant risk score for allograft failure	6129	16 y	Web-based	Multivariable Cox model	System/patient improvement	Yes	Yes	Quantitative	NI

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TABLE 2. (Continued)

Paper details		Study design												
Author	Year	Study type	Study country of origin, number of centers	Organ	Study period	Study aim	Patient number	Follow-up	CDSS used	Methodology of CDSS	Type of outcome (ie, economic, system improvement, patient improvement)	Overall improvements? (Y/N)	Results validation comparison with usual care	Validation end point(s) category	Validation statistical significance
Patzer et al[60]	2018	Randomized trial	USA, 3 US kidney transplant centers	Kidney	December 2014 to October 2015	To study the effectiveness of CDSS in improving transplant knowledge in patients undergoing evaluation for transplant	443	3 mo	Web-based	Regression	Improve patient's knowledge and understanding of treatment choices	Yes	Yes	Qualitative	Yes

CDSS, clinical decision support system; NI, no information; RCT, randomized control trial.

applications to allow the user to engage in self-care activities in the early stage of posttransplantation. Many of the CDSS tools allowed users to also engage in shared patient message boards and send communication directly to their transplant healthcare team such as recorded telemetry data through personal devices (ie, blood pressure home monitoring). In turn, their data were used by the healthcare team to make decisions about the patients such as instigating a review of the patient in clinic based on the data received. For instance, the tool created by Finkelstein et al monitored patient's post lung transplant recovery via home spirometry measurements that were then transmitted directly to the transplant team. In addition, patients were able to upload messages regarding their perceived symptoms to the healthcare team.[21] Finally, some of the CDSSs in this category expanded the use of the tool to include transplant patients' family members.[15]

User Interface

Eleven studies utilized a mobile application, front-end design. This was described as an especially important feature within those CDSSs that were aimed at helping patients engage in self-care activities. As these were almost exclusively carried out in a nonclinical setting, it was essential that these CDSSs allowed patients a convenient, easy, and cost-effective method for staying involved in their posttransplant monitoring. Four studies combined the use of a portable spirometry device to allow home-monitoring of post–lung transplant patients. Due to the age of 2 of the CDSS tools that utilized spirometry, 1 study published in 1999 and the other in 2002, some of the technology design elements would need to be reconfigured if applied to current day design as modems were used to transmit patient data gathered from their devices at home and sent back to transplant teams.[16,22]

CDSS Type

Seventeen of the studies utilized a non–knowledge-based approach to the design of their CDSS. The high number of tools based on this particular approach may be linked to the nature of the clinical purpose—providing patients with a tool to provide basic clinical feedback to their medical teams in a timely, efficient, and easy-to-use manner. Three CDSS tools were based on knowledge-based design and only 1 tool by Finkelstein employed Bayesian models. The tool created by Finkelstein's group focused on post–lung transplant patients and created a set of "watch" criteria for these patients based on symptoms and results of home spirometry collected during another study. These criteria were then used to develop the computerized triage rules that informed the training data set. An independent set of retrospective home-monitoring data was used for testing. Finally, a prospective group of transplant patients was used to evaluate the home-monitoring data using latent class analysis. The decision system classified the weekly data results from the patients as 1 = "watch" (requiring potential clinical follow-up) or 0 = "no watch." This tool aimed to review the relative performance of their CDSS tool compared with manual nurse-led decision-making for triaging clinical intervention of lung transplant recipients.[21] The 3 knowledge-based CDSS tools provided a variety of clinical interventions. The tool by Garthwaite et

TABLE 3.

Waitlist management

Paper details		Study design														
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient number**	**Follow-up**	**CDSS used**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Statistical significance (yes/no)**	**Overall improvement, yes/no?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Cheng et al[56]	2018	Prospective cohort	Single center, Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, California	Kidney	December 2014 to June 2017	To assess the Kidney Allocation System score to approach the preparedness of patients near the "top of the list" in a more systematic fashion using a novel wait-list management process	195	18 mo	Computer-based	Bayesian methods	System improvement/patient improvement	Yes	Yes	Yes	Quantitative	Yes
Gambato et al[57]	2007	Prospective cohort study	Single center, University of Padua, Padua, Italy	Liver	July 2004 to June 2006	To test the feasibility of using an algorithm based on 7 patient variables to prioritize liver patients on the waiting list	118	2 y	Computer-based	Knowledge-based	Patient improvement	Yes	Yes	No	Quantitative	Yes

CDSS, clinical decision support system.

TABLE 4.

Immunosuppressant management

Paper details	Study design														
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient numbers**	**Follow-up**	**CDSS**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall clinical improvement, yes/no?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Åsberg et al[31]	2010	Pilot study (RCT)	Renal Physiology, Rikshospitalet, Oslo, Norway (single center)	Kidney	August to December 2008	The aim was to compare accuracy of experienced clinicians against a computer-assisted dosing model	40	47 to 100 d after transplantation	Computer-based	Bayesian methods	System improvement/ patient improvement	Yes	No	Quantitative	NI
Cremers et al[32]	2003	Prospective cohort	Leiden University Medical Center, Leiden, The Netherlands	Kidney transplant alone, simultaneous pancreas kidney transplant	Not stated	Validate a limited sampling strategy, based on a compartmental population pharmacokinetic model for transplant recipients	60	12 h	Computer-based	Bayesian methods	System improvement	Yes	No	Quantitative	NI
Dobbels et al[33]	2017	Randomized controlled trial	University Hospitals of Leuven, Belgium	Heart, liver, and lung	Not stated	To test the efficacy and sustainability of a 6-mo multicomponent tailored medication adherence enhancing intervention in adult heart, lung, and liver transplant recipients	247	15 mo	Computer-based	Nonknowledge	Patient and system improvement	Yes	Yes	Quantitative	Yes

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TABLE 4. (Continued)

Paper details	Study design														
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient numbers**	**Follow-up**	**CDSS**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall clinical improvement, yes/no?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Eisenberger et al[20]	2013	Prospective cohort	5 study sites in Switzerland	Kidney	May and August 2011	To evaluate the accuracy of the ingestible sensor system for directly assessing the ingestion of oral medications and treatment adherence	22	~9 wks	Mobile app-based	Nonknowledge	Patient improvement	Yes	No	Quantitative	NI
Foster et al[35]	2018	Unblinded, parallel-arm randomized trial	8 pediatric transplant programs in Canada and the United States	Kidney	February 2012 to May 2016	To determine if electronic monitoring increased patient adherence taking antirejection medication	81	15 mo	Web-based	Nonknowledge	Patient improvement	Yes	Yes	Quantitative	Yes

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TABLE 4. (Continued)

Paper details	Study design						Patient numbers	Follow-up	CDSS	Methodology of CDSS	Type of outcome (ie, economic, system improvement, patient improvement)	Overall clinical improvement, yes/no?	Results validation comparison with usual care	Validation end point(s) category	Validation statistical significance
Author	Year	Study type	Study country of origin, number of centers	Organ	Study period	Study aim									
Francke et al[37]	2021	Prospective cohort	Erasmus MC, University Medical Center Rotterdam, The Netherlands	Kidney	Between February 23, 2019, and July 7, 2020	To increase the percentage of patients with a tacrolimus within the therapeutic range and to minimize the occurrence of tacrolimus underexposure and overexposure in the early phase after renal transplantation by using a dosing algorithm	60	30 d	Computer-based	Knowledge-based	Patient and system improvement	No	No	Quantitative	No
Fukudo et al[36]	2009	Cohort study	Kyoto University Hospital, Japan (not explicitly stated)	Living-donor liver transplantation (LDLT)	Not stated	To assess the clinical applicability of the Bayesian method to calculate tacrolimus requirements in transplant patients	40	4 wks	Computer-based	Bayesian methods	System improvement	Yes	Yes	Quantitative	Yes

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TABLE 4. (Continued)

Paper details	Study design						Patient numbers	Follow-up	CDSS	Methodology of CDSS	Type of outcome (ie, economic, system improvement, patient improvement)	Overall clinical improvement, yes/no?	Results validation comparison with usual care	Validation end point(s) category	Validation statistical significance
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**									
Geramita et al[22]	2020	Prospective cohort	University of Pittsburgh Medical Center (UPMC), USA (single center)	Lung	January 2009 through December 2011	To assess whether the mobile app has sustained effects on lung transplant recipients' medical regimen adherence beyond the 1-y period posttransplant	N/A	2.5 y	Mobile app-based	Nonknowledge	Patient/system improvement	Yes	Yes	Qualitative	Partially
Henriksson et al[43]	2016	RCT	Karolinska University Hospital in Stockholm, Sweden (single center)	Renal	1 June 2011 to 30 June 2013	To use the electronic medicine dispenser to study patient compliance with immunosuppressive medications	80	1 y	Web-based	Nonknowledge	Patient/system	Yes	Yes	Qualitative, quantitative	Yes
Jung et al[44]	2020	Prospective, multicenter, randomized controlled study	South Korea	Kidney	Not stated	Evaluate the efficacy and stability of an information and communication technology–based centralized monitoring system for increasing medication adherence among Korean kidney transplant recipients	114	6 mo	Web-based	Nonknowledge	Patient and system improvement	No	Yes	Qualitative, quantitative	No

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TABLE 4. (Continued)

Paper details	Study design														
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient numbers**	**Follow-up**	**CDSS**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall clinical improvement, yes/no?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Le Meur et al[45]	2007	Open-label, RCT	France, 11 centers	Kidney	12 mo	Evaluate the performances of an MMF dosing system, based on a Bayesian estimator of MPA applied to renal transplants recipients	137	1 y	Computer-based	Bayesian methods	System/patient improvement	Yes	Yes	Quantitative	Yes
Levine et al[46]	2019	RCT	USA, single center	Deceased donor renal transplant, living donor renal transplant, simultaneous pancreas-kidney transplant, or liver-kidney transplant	Between January 2015 and December 2016	To test whether a mobile app (Transplant Hero) targeting multiple levels of risk factors for nonadherence can increase immunosuppressive medication adherence in adult kidney, pancreas, and/or liver transplant recipients	108	3 mo	Mobile app-based	Nonknowledge	Patient outcome	No	Yes	Quantitative	No

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TABLE 4. (Continued)

Paper details	Study design														
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient numbers**	**Follow-up**	**CDSS**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall clinical improvement, yes/no?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
McGillicuddy et al[47]	2020	Prospective, parallel-arm, randomized controlled trial	Medical University of South Carolina, Charleston, SC, USA, single center	Kidney	12-mo study period, dates unknown	Was to determine if mobile health (mHealth) intervention aimed at improving medication adherence in a nonadherent kidney transplant population would affect high intrapatient tacrolimus variability	80	1 y	Mobile app-based	Nonknowledge	System/patient improvement	Yes	Yes	Quantitative	Yes
Reese et al[49]	2017	Randomized controlled trial	Hospital of the University of Pennsylvania, USA (Implemented in single center)	Kidney	February 2012 through March 2014	Determine whether automated reminders in cases of low adherence improve tacrolimus adherence compared to adherence monitoring alone	120	6 mo	Computer-based	Nonknowledge	System/Patient improvement	Yes	Yes	Qualitative, quantitative	Yes

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TABLE 4. (Continued)

Paper details	Study design														
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient numbers**	**Follow-up**	**CDSS**	**Methodology of CDSS**	**Type of outcome (ie, economic, system improvement, patient improvement)**	**Overall clinical improvement, yes/no?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Rosenberger[50]	2017	RCT	University of Pittsburgh Medical Center, USA, one center	Lung	lung transplant recipients during their hospitalization for transplantation between January 2009 to December 2012	To examine whether access to Pocket PATH during the first year after transplant was associated with reduced risk of mortality and bronchiolitis obliterans syndrome	n/a	1 y	Mobile app-based	Nonknowledge	Patient improvement	No	Yes	Qualitative, quantitative	No
Størset et al[52]	2015	RCT	Oslo University Hospital Rikshospitalet, Norway	Kidney	From 13 January to 9 June 2014	To prospectively evaluate the target concentration achievement of tacrolimus using computerized dosing compared with conventional dosing performed by experienced transplant physicians	80	8 wks	Computer-based	Knowledge-based	System/patient improvement	Yes	Yes	Quantitative	Yes

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TABLE 4. (Continued)

Paper details	Study design														
Author	Year	Study type	Study country of origin, number of centers	Organ	Study period	Study aim	Patient numbers	Follow-up	CDSS	Methodology of CDSS	Type of outcome (ie, economic, system improvement, patient improvement)	Overall clinical improvement, yes/no?	Results validation comparison with usual care	Validation end point(s) category	Validation statistical significance
Tang et al[53]	2017	Prospective cohort	The Third Xiangya Hospital of Central South University and Peking University Health Science Center, China	Kidney	October 2012 and September 2014	To compare the performance of multiple linear regression and eight machine learning techniques in pharmacogenetic algorithm-based prediction of tacrolimus stable dose	1045	Not stated	Computer-based	Other ML techniques	System/patient improvement	Yes	No	Quantitative	Yes
Tecen-Yucel et al[54]	2020	Prospective cohort	University Research & Training Hospital, Ankara, Turkey	Kidney	November 2017 and February 2018	To characterize the difference in severity levels of drug interactions with tacrolimus and cyclosporine provided by 3 drug interaction programs in renal transplant recipients	80	No follow-up, data conducted during single clinic visit for patient	Computer-based	Other ML techniques	System/patient	No	Yes	Quantitative	No
Zanetti-Yabur et al[55]	2017	Prospective cohort	Montefiore-Einstein Center for Transplantation, NY, USA	Kidney, liver	6-mo period beginning June 2015	To investigate the efficacy of users and nonusers of a mobile app in promoting medication adherence	74	3 mo	Mobile app-based	Nonknowledge	Patient/system improvement	No	Yes	Qualitative, quantitative	No

CDSS, clinical decision support system; ML, machine learning; MMF, mycophenolate mofetil; MPA, mycophenolic acid; NI, no information.

TABLE 5.

Interpretation of histopathology

Paper details		Study design													
Author	**Year**	**Study type**	**Study country of origin, number of centers**	**Organ**	**Study period**	**Study aim**	**Patient numbers**	**Follow-up**	**CDSS**	**Methodology of CDSS**	**Type of outcome**	**Overall clinical improvement?**	**Results validation comparison with usual care**	**Validation end point(s) category**	**Validation statistical significance**
Marsh et al[63]	2018	Prospective cohort	Single center, USA	Kidney	April 2015 to July 2017	Evaluate the performance of deep learning variants applied to the problem of glomerular identification and classification in renal preimplantation frozen section wedge biopsies	17	Not specified	Computer-based	Deep learning	System improvement	Yes	No	Quantitative	NI
Yi et al[62]	2022	Prospective cohort	2 cohorts: one multicenter in USA, one Australian)	Kidney	Not mentioned	Detect pathological lesions from baseline or posttransplant biopsies and predict risk of posttransplant graft loss	616	Median duration of 4.5 y	Computer-based	Deep learning	System/patient improvement	Yes	No	Quantitative	NI

CDSS, clinical decision support system; NI, no information; RCT, randomized control trial.

al provided transplant doctors with a prompt to instigate cholesterol management in renal transplant patients during follow-up clinics.[38] Staes et al also created a prompting tool; however, their tool focused on processing transplant patient laboratory reports.[51] Finally, Wang et al's knowledge-based tool provided an automated decision system to detect clinically important bronchopulmonary events in lung transplant patients.[29]

Clinical Endpoints

The majority of the clinical endpoints within this group of CDSS studies looked at shorter-term outcomes. However, a few of the studies had longer-term outcomes (range: 1 to 2 y).[21,23,38,48] A number of the clinical endpoints examined not only outputs used to help determine a patient's health posttransplant, but many also incorporated psychosocial aspects into their endpoints including Dew's psychosocial intervention program to improve the mental health and quality of life (QoL), Dabb's tool, Pocket PATH to promote self-care behaviors, and Lerret's smartphone app to improve postdischarge outcomes of coping, family QoL, self-efficacy, and family self-management.

Graft Survival Prediction

General Overview

Four studies examined tools to assess graft survival risk pre- or posttransplant, where the predictions were used to inform clinical care in a real patient cohort.[49-53] These studies exclusively examined the risk in kidney transplant recipients. Several of these tools focused on creating implementable risk prediction scores for kidney transplant failure. For example, Loupy et al generated a posttransplant risk prediction score (the iBox) that allows guided monitoring of patients, with changes in predicted survival prompting an alert to guide further investigation or change in management.[49]

User Interface

Three of the 4 tools within the graft survival prediction risk category used a web-based approach to their front-end development.[58,60,61] This design may have been selected by transplant teams to help assist clinicians to access patient data to input into the tools. For example, in the iChoose Kidney CDSS clinicians could input patient data and also access the tool quickly on a web-based application, to discuss survival benefits and risks of a transplant to patients in a clinical setting as described by Patzer et al.

CDSS Type

All 4 CDSSs within this category used a back-end design that incorporated regression models into the tools. Three of the 4 studies utilized a regression model based on Cox-proportional hazard ratios,[58,59,61] and the other study used logistic regression.[60]

Clinical Endpoints

The majority of studies used time to graft failure as an endpoint, with slightly different variants of time until loss being studied. Patzer et al differed from the other studies in this group as their endpoint was change in patient knowledge about the survival benefits of kidney transplant and access to kidney transplant. Several of the studies assessed risk at various time points; however, Aubert et al looked at the risk of graft failure at up to 11 y, which was the longest time period of all studies in this category.[59]

Waiting List Management

General Overview

Four studies investigated CDSSs designed to inform waiting list management of transplant patients. Cheng et al and Gambato et al both utilized newer, knowledge-based CDSSs to address clinical problems with the waiting list for kidneys and livers, respectively.[56,57] Cheng described their American center's tool, which aimed to address the rising proportion of deceased donor kidney transplant candidates that were listed as inactive for transplant while awaiting a complete transplant evaluation work-up. The tool would score those patients that were likely to be called for transplant by UNOS in the near term (based on the tool's predictive modeling), so the transplant team could call them back to clinic to ensure all evaluative testing and work-up was up to date. This was especially relevant to their center's patient population, who often lived far from the center and did not have up-to-date bloods, cardiology testing, and other required information for UNOS. Alternatively, Gambato et al's tool provided clinicians with an algorithm to prioritize liver transplant patients on the waiting list in their Italian center during 2004 to 2006. Furthermore, the team used the tool to prospectively evaluate cirrhotic patients with and without hepatocellular carcinoma undergoing liver transplant and reviewed their mortality while on the waiting list and following transplant. Gambato et al used slightly longer end points at 24 mo and focused on a specific subset of transplant patients, cirrhotic liver patients. Conversely, Cheng et al used 18 mo as study endpoints and included all patients awaiting kidney transplant within their center.

User Interface

Both CDSS utilized a web-based user interface design. Cheng et al integrated their tool with their institution's Transplant Readiness Assessment Clinic's (TRAC) Kidney Allocation Score to fast-track kidney transplant patients for clinic work-up to ensure readiness for transplant, making a web-based design easier to use with their pre-existing system. Gambato et al, similarly to Cheng et al, had a single-center institution and were using the CDSS as a way to approach patients with long transplant waiting times in their center.

CDSS Type

Cheng et al and Gambato et al both used a knowledge-based approach to their CDSS design. The specific knowledge-based design differed between the 2 studies. Cheng et al utilized the Kidney Allocation System score as a sum of wait-time in years (secured from UNOS qualifying date) and additional points derived from a sensitization sliding scale. Gambato et al selected clinical variables (The Child-Turcotte-Pugh score [CTP] and the model for end stage liver disease [MELD], Hepatic Cellular Carcinoma status, and body mass index, time on waiting list, and age) to construct their algorithm.

Clinical Endpoints

Through Cheng et al's TRAC CDSS approach, their team aimed to produce a more streamlined clinical pathway for patients awaiting work-up for transplant (especially for centers with very large waiting lists). Following the use of their tool, Cheng et al's center had a higher proportion of patients on the waitlist as illustrated at the 18-mo mark where TRAC patients were more likely to be actively listed on the UNOS waiting list (38% versus 22%–26%, $P < 0.0001$) in comparison with the historic patient population (usual waitlist prioritization who were still awaiting clinical evaluations before listing on the UNOS system). Finally, Gambato et al found that MELD may be a useful tool in prioritizing patients on the waiting list as their results showed that 24-mo patient survival was significantly lower among patients with MELD >25 (57%) compared to patients with MELD < 25 (MELD: 0–15 = 87%, 16–25 = 92%, $P = 0.017$).

Interpretation of Histopathology

General Overview

Last, 2 tools by Yi et al and Marsh et al were designed to interpret histopathology posttransplant.[62,63] Both groups used image analysis of posttransplant biopsies to help identify pathological lesions predictive of graft outcomes. Yi et al created a model to identify mononuclear leukocyte infiltration and pathological lesions in the interstitium and tubules within kidney transplants. Marsh et al also looked at kidney transplant biopsies; however, they focused on preimplantation donor biopsies to determine kidneys suitable for transplant by reviewing the percent of glomeruli that were normal versus sclerotic. This ratio provides one of the key factors in indicating the transplant outcome.

User Interface

Both CDSSs were constructed to display results via a web-based user interface design. However, neither study described in detail the front-end design nor the requirements to implement such a system within their pre-existing clinical workspaces. The main description in both articles focused on the computing design of the CDSSs.

CDSS Type

Yi et al and Marsh et al were the only 2 studies within the review that utilized a DL approach to create their backend infrastructures. To do so, they relied on convolutional neural networks (CNNs), a type of DL, neural architecture that is popular for image analysis. Marsh et al used digitized frozen sections of glomeruli and had 2 pathologists annotate the sclerosed glomeruli on the images. These annotations were then used for testing and training the CNNs. Marsh et al's group utilized image patches that were centered on the pathologist labeled sclerotic and nonsclerotic glomerulus. Another 1932 random regions were selected that contained no glomeruli were extracted for training the model on the tubulointerstitial areas. This training set was further changed to include rotations, image flipping and small translations.

Marsh et al created a classical feed-forward network, while Yi et al adapted 2 novel CNN architectures: Mask R-CNN and U-Net.[64,65] Mask R-CNN allows the CNN execution by predicting regions of interest. U-Net is a convolutional autoencoder intended to perform semantic image segmentation. The group then compared these predicted results with the annotations made by clinicians and the results were compared by true positive rate and positive predictive values. Following the training of the DL models based on Mask R-CNN and U-Net to recognize the normal verses abnormal region of the tissue, Yi et al extracted whole slide-wide features to ensure that abnormal interstitium, tubules, and inflammation were identified. This allowed the comparison with the baseline Banff scores and posttransplant graft survival.

Clinical Endpoints

Yi et al demonstrated that their DL model was able to accurately detect pathological lesions (compared with baseline). Furthermore, their tool demonstrated superior ability for prediction of posttransplant graft loss when compared to an expert pathologist. Although Marsh et al did not find superiority in their DL tool compared to expert renal pathologists, they did show that their extended model performed on par with experts when reviewing whole slide images of renal biopsies taken before transplantation.

Validation of CDSSs

Of the included CDSS papers, just over half of the studies validated their tool against standard clinical care (n = 29, 60.4%). Twenty-two of the tools achieved statistical significance through their validation testing (45.8%) (Tables 1–5).

DISCUSSION

This review of CDSS utilized in transplant medicine has identified a number of areas where both knowledge-based and non–knowledge-based CDSSs may be beneficial in guiding the management of patients both pre- and posttransplant. Areas of use include immunosuppression management, pretransplant risk assessment, and interpretation of histopathology. However, it has also highlighted the heterogeneous and often inconsistent reporting of the CDSS' impact on clinical and system outcomes. Furthermore, there has been limited information validating these tools in clinical practice. Although there are some studies in the medical literature that attempt to predict graft survival utilizing mathematical algorithms, such as the Kidney Donor Profile Index or Donor Risk Score, none of them utilized digital or computerized aids. Anecdotally, there is evidence that these algorithms are used in clinical practice; however, there have been no published clinical studies to date using these algorithms in a prospective, clinical setting.

The design of the CDSS studies within this review tended to be low quality and were often coupled with a high risk of bias. Many of the studies did not include descriptors of strategies to fully implement the tool within clinical practice, seeming to trial it prospectively in patient groups for academic purposes without steps in place to roll out the CDSS further. Of the 19 smartphone applications described in our review, only 5 applications had funding or input from commercial entities (including pharmaceutical companies or spin out companies). Of the remaining 14 smartphone applications, no description of commercial development existed and they were funded largely by government or charitable organizations. Finally, an even larger

number of CDSS and predictive models reported in the literature were not eligible for inclusion in this review as they have not been used prospectively in real patient cohorts to assess their clinical impact.

Many devices identified were built without consideration for end-user or patient feedback. Developers of the applications may be missing an invaluable opportunity to engage with the end users of these CDSS tools further by completing user testing and trialing of the device for direct feedback into both the design and functionality of these devices. A better understanding of these facets of the tools would allow for the creation of more specific and individualized user interface designs. Research by Rawson et al specifically identify these factors as imperative in developing future CDSSs by including predeployment stakeholder engagement including the clear construction of goals and clinical objectives of the CDSS, workflow analysis, and ensuring seamless integration of the CDSS into pre-existing clinical systems.[66] The design process of these tools should be a cyclical process with continued re-evaluation and reassessment of underlying decision models and user interfaces.

Another major barrier to implementation of many CDSSs into the clinical environment lies in challenging regulatory pathways for clinicians to navigate. CDSS tools in many countries are classified as a medical device, which require their design to meet stringent criteria for marketing use and ultimately may act as a barrier to clinical implementation.[67] However, despite these challenges, governmental bodies are implementing programs to help bring many of these tools to clinical use as they recognize the value of these newer technologies to creating after clinical care. For instance, the National Institute for Health and Care Excellence, has created a multiagency advisory service to enable the development and clinical implementation of innovative technologies, ultimately recognizing the unparallel advantage such tools can have to patients.[68]

As well as navigating the regulatory landscape, architects of CDSSs must also consider the integration of these into existing systems, including EMRs that are already being used within a clinical setting. As more and more transplant centers rely on electric offering data as well as other data sources for transplant donors and recipients, the integration of these pre-existing systems into a CDSS is a vital necessity, not a "nice to have" feature. For instance, in a usability study by Devine et al testing a CDSS prescribing tool with clinicians, the auto-population mechanism was specifically cited as a very useful feature.[69] Manual data entry is not only time-consuming and a barrier to use but also a potential point of failure due to transcription error.

The ultimate test of the usability, usefulness, and impact on clinical outcomes of CDSSs is testing these systems in clinical trials. A large number of transplant-related tools or predictive models (especially as new technologies in AI emerge) are being created; however, the pipeline for implementing these tools into clinical practice is extremely sparse.[70–73] They are generally not implemented in a prospective manner in real patient cohorts to assess the impact of these tools on clinical outcomes. Furthermore, especially within the AI-based CDSS tools, there is sparse analysis of the explainability of these tools and individualized analysis of end-user requirements for the transparency of such clinical programs.[74]

Potential CDSSs should be evaluated and tested in prospective RCTs carried out in real-world clinical environments to ensure the full review of benefits and any barriers to implementation. The National Institutes of Health Pragmatic Trials Collaborative suggests that another hurdle to creating meaningful CDSS trials lies with the patient acting as the unit of randomization and the clinician interacting with only the tool in RCTs. The group suggests cluster randomization as a solution to this issue but point out that the sample size required for this may become a challenge unless large trials are conducted.[75] Finally, Wright et al have proposed a study architecture to lead the implementation and design of such RCTs in CDSS tools. Their proposed 4-phase model focuses on defining a clear set of desirable features of the tool, building a prototype of the CDSS, demonstrating the usefulness of the tool through its integration into existing systems, and comparing its functionality to other proposed models.[76]

Limitations

Like other systematic reviews on CDSSs, the main limitation of our study and subsequent analysis was the high level of heterogeneity among the types of CDSS research articles included and a wide variety of outcomes measures included.[77] Part of the reason for this heterogeneity is likely the broad nature of the inclusion criteria for this review which included a number of clinical outcomes, settings, CDSS tool architecture, and study designs. Finally, it is important to note that the technology landscape of CDSS tools are rapidly evolving and the review papers included were evaluated as they exist today. In many cases, there will be ongoing research and new CDSS tools under development but not fully researched that may address some of the limitations we describe in terms of validation and high bias levels.

CONCLUSIONS

Some reviews examining CDSSs have called for a complete re-examination of the role that CDSSs play in clinical care,[78] whereas other researchers note that the future of CDSS effectiveness may lie in integrating the technology more seamlessly into EHRs or creating more innovative approaches to the design of the tools by incorporating ML into CDSSs that may benefit from the technology.[25] As with other frequently seen, common interventions in medicine such as checklists or treatment bundles, it is important that the way the CDSS would actually work and to what degree that is would actually target the clinical problem be fully evaluated before the design.

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