Effectiveness of eHealth on medication adherence in kidney transplant recipients: systematic review and meta-analysis

Lili Zhou, Linbin Chen, Xinyi Hou, jingjing Wan

Submitted to: Journal of Medical Internet Research
on: March 06, 2025

Table of Contents

Effectiveness of eHealth on medication adherence in kidney transplant recipients: systematic review and meta-analysis

Lili Zhou[1]; Linbin Chen[2]; Xinyi Hou[1]; jingjing Wan[3]

[1] Xiangya College of Nursing, Central South University changsha CN
[2] Xiangya College of Nursing, Central South University Xiangya College of Nursing, Central South University changsha CN
[3] Outpatient Operating Room, Nuring Department of Xiangya Third Hospital of Central South University changsha CN

Corresponding Author:
Lili Zhou

Xiangya College of Nursing, Central South University
Xiangya College of Nursing, Central South University
changsha
CN

Abstract

Background: Compared to conventional outpatient or telephone follow-up, the introduction and use of eHealth technologies provide novel opportunities for enhancing medication adherence in transplant recipients. Nonetheless, the efficacy of eHealth treatments regarding medication adherence in kidney transplant recipients remains ambiguous.

Objective: To assess the impact of eHealth interventions on medication adherence in kidney transplant recipients and to understand the underlying factors.

Methods: Seven databases (PubMed, Web of Science, Cochrane, Embase, CINAHL, SCOPUS,and OVID) were thoroughly checked from the beginning till November 2024. Each study was assessed for bias using the Cochrane Risk of Bias tool (RoB 2), and the certainty of the evidence for each outcome of interest was rated using the GRADE criteria.The study outcomes were evaluated using a narrative synthesis and a meta-analysis.

Results: A total of 12 studies involving 897 kidney transplant recipients were included. The eHealth intervention improved medication adherence monitored by electronic devices compared with the control group [RR=1.46, 95% CI (1.11, 1.90)]. However, the differences in adherence to medication as assessed by the Basel Immunosuppressive Medication Adherence Scale [RR=0.98, 95% CI (0.85, 1.13)], tacrolimus blood concentration [MD=0.15, 95% CI (-0.21, 0.51)], and intra-patient variability of tacrolimus [MD=-0.02, 95% CI (-0.07, 0.03)] were not statistically significant. The overall risk of bias was very high or some concerns, and the evidence for all outcomes was of low quality.

Conclusions: The true effectiveness of eHealth interventions is affected by a variety of confounding factors, and more high-quality future studies are still needed to optimise eHealth intervention strategies and clarify their effectiveness in improving medication adherence. Clinical Trial: PROSPERO CRD42025640638; https://www.crd.york.ac.uk/PROSPERO/myprospero

(JMIR Preprints 06/03/2025:73520)
DOI: https://doi.org/10.2196/preprints.73520

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http
No. Please do not make my accepted manuscript PDF available to anyone.

Original Manuscript

Paper type:
systematic review and meta-analysis

Title:
Effectiveness of eHealth on medication adherence in kidney transplant recipients: systematic review and meta-analysis

Authors:
Lili Zhou[1], Linbin Chen[1], Xinyi Hou[1], Jingjing Wan[2]
[1]Bachelor's degree, Xiangya College of Nursing, Central South University, Changsha, Hunan, China.
[2]Bachelor's degree, Outpatient Operating Room, Nuring Department of Xiangya Third Hospital of Central South University, Changsha, Hunan, China.

Corresponding author:
Jingjing Wan (Email:1442538244@qq.com, Tel:13975129976)

Author disclosures:
Study concept and design: Lili Zhou and Jingjing Wan
Acquisition of data□Lili Zhou and Linbin Chen
Analysis and interpretation of data: Lili Zhou, Linbin Chen and Xinyi Hou
Drafting of the manuscript: Lili Zhou
Critical revision of the manuscript for important intellectual content: Jingjing Wan

Tip: Do not want automatic transfer to other journals

Effectiveness of eHealth on medication adherence in kidney transplant recipients: systematic review and meta-analysis

Abstract

Background
Compared to conventional outpatient or telephone follow-up, the introduction and use of eHealth technologies provide novel opportunities for enhancing medication adherence in transplant recipients. Nonetheless, the efficacy of eHealth treatments regarding medication adherence in kidney transplant recipients remains ambiguous.

Objective
To assess the impact of eHealth interventions on medication adherence in kidney transplant recipients and to understand the underlying factors.

Methods

Seven databases (PubMed, Web of Science, Cochrane, Embase, CINAHL, SCOPUS,and OVID) were thoroughly checked from the beginning till November 2024. Each study was assessed for bias using the Cochrane Risk of Bias tool (RoB 2), and the certainty of the evidence for each outcome of interest was rated using the GRADE criteria.The study outcomes were evaluated using a narrative synthesis and a meta-analysis.

Results
A total of 12 studies involving 897 kidney transplant recipients were included. The eHealth intervention improved medication adherence monitored by electronic devices compared with the control group [RR=1.46, 95% CI (1.11, 1.90)]. However, the differences in adherence to medication as assessed by the Basel Immunosuppressive Medication Adherence Scale [RR=0.98, 95% CI (0.85, 1.13)], tacrolimus blood concentration [MD=0.15, 95% CI (-0.21, 0.51)], and intra-patient variability of tacrolimus [MD=-0.02, 95% CI (-0.07, 0.03)] were not statistically significant. The overall risk of bias was very high or some concerns, and the evidence for all outcomes was of low quality.

Conclusions
The true effectiveness of eHealth interventions is affected by a variety of confounding factors, and more high-quality future studies are still needed to optimise eHealth intervention strategies and clarify their effectiveness in improving medication adherence.

Trial Registration
PROSPERO CRD42025640638; https://www.crd.york.ac.uk/PROSPERO/myprospero

Keywords
eHealth, interventions, kidney transplantation, medication adherence, systematic, meta-analysis

1. Introduction

In 2023, the World Health Organisation (WHO) and the Global Observatory for Organ Donation and Transplantation (GODT) reported approximately 170,000 organ transplants worldwide that year, with kidney transplants being 64.46% of this total [1]. Kidney transplantation, the optimal treatment for end-stage renal failure, has a 1-year postoperative graft survival rate above 95%, markedly enhancing patients' quality of life relative to dialysis [2]. Nonetheless, its long-term prognosis is unfavourable, with a 10-year graft survival rate potentially declining to 67.8% [3].

Poor medication adherence is an independent risk factor for this adverse outcome. Reports indicated that about 15.5% to 57.5% of kidney transplant recipients have irregular medication-taking behaviour, and adherence decreases by 4.8% per year after transplantation [4,5]. Inadequate medication adherence can increase the likelihood of transplant renal failure by seven times and death by threefold [6]. Conventional adherence therapies (e.g., in-person teaching, outpatient follow-up, or telephone reminders) are constrained by spatial and temporal accessibility, labour expenses, and passive patient engagement.

In recent years, eHealth technologies have provided innovative ways to address this issue through short message services, mobile applications, wearable devices, and artificial intelligence-assisted systems [7]. Their core strengths are real-time, personalised, and interactive. The smart pillbox reminder function enables accurate medication timing control [8,9]; the electronic log monitors medication adherence in real time, while the algorithm-driven feedback system analyses adherence data and offers personalised health recommendations [10,11]. Meta-analyses have shown that eHealth is useful in improving medication adherence in patients with chronic conditions (e.g., cardiovascular, stroke) [12,13], but evidence in the kidney transplant population is sparse. Tang et al. [7] demonstrated that short-term eHealth interventions enhance medication adherence and self-regulatory behaviours in solid organ transplant recipients (liver, kidney, lung, and heart), but fewer studies will assess long-term biochemical outcome metrics, such as the stability of tacrolimus trough concentrations. In addition, medication adherence is a dynamic process influenced by multiple factors (e.g., patient engagement, forgetfulness, medication beliefs), which may affect the actual effectiveness of eHealth interventions [14,15], highlighting the importance of evidence-based medicine in detecting confounding factors and optimising intervention strategies.

This study combines objective bioindicators (e.g., coefficient of variation [CV] of blood concentration of tacrolimus) and subjective behavioural data, with the goal of systematically evaluating the effectiveness of eHealth interventions in improving medication adherence in kidney transplant recipients and exploring the related potential interfering factors, so as to provide scientific bases for the development of precise and sustainable e-medication adherence management programs.

2. Methods

2.1. Design

The study received approval from PROSPERO, with protocol registration number CRD42025640638 dated 31/01/2025. We conducted the assessment according to the PRISMA guidelines. Review studies do not require ethical approval from the author's institution.

2.2. Search strategy

Before data collection, we developed the research questions utilizing the PICOS (Population, Intervention, Control, Outcome, Research Design) framework. Thereafter, keywords were derived from the research questions, with English keywords sourced from MeSH (Medical Subject Headings). The search terms encompassed keywords such as 'kidney transplantation,' 'medication adherence,' 'telemedicine,' 'smartphone,' 'mobile applications,' 'internet,' 'self-management,' and 'randomized controlled trial.' The specified keywords and concepts were thoroughly investigated in seven electronic databases (PubMed, Embase, Web of Science, CINAHL, SCOPUS, OVID, and the Cochrane Library) for articles from the inception of each database to November 19, 2024 (Supplementary). Furthermore, we conducted a thorough examination of the references included in this review paper to identify other sources.

2.3. Study eligibility criteria

Inclusion criteria were as follows: (i) The target population was kidney transplant recipients on immunosuppression. (ii) Study type was a randomized controlled trial. (iii) The intervention group receives eHealth interventions, which are defined as those administered by diverse information and communication technologies, including phone calls, text messaging, telemedicine (e.g., videoconferencing), websites, and mobile applications. (iv) The control group receives standard care that excludes e-interventions aimed at enhancing drug adherence. (v) The outcome indicator is the level of medication adherence in kidney transplant recipients, measured by both objective and subjective measures [16]. Objective measures: medication adherence tracked by electronic devices, tacrolimus blood concentration, Intra-patient variability (IPV) of tacrolimus concentrations (typically represented as CV and calculated as [Mean /SD] × 100%), and the percentage of patients exhibiting a tacrolimus CV<40%. (Henriksson et al. [17] and Mansell et al. [18] have validated the use of 40% as the threshold to distinguish between normal and elevated IPV). Subjective measurements were self-report questionnaires, including the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS), the Immunosuppressive Medication Adherence Scale (IMAS), and the Medical Adherence Measure Medication Module (MAM-MM). We excluded studies with trial protocols, solely published abstracts, or lacking full text.

2.4. Data partitioning

The Endnote software was utilized to archive scanned papers and eliminate duplicate copies. Two reviewers individually assessed the titles and abstracts to identify papers that potentially satisfied the inclusion criteria. The complete texts of the articles were acquired and examined. Disputes were resolved through dialogue. The PRISMA flowchart (Figure 1) provides a brief overview of the screening process. We extracted all relevant data on participant characteristics, interventions, and outcome metrics. The features included the first author's name, year of publication, country, sample size, average patient age, study, intervention content, intervention duration, measurement points, and outcome measurements.

2.5. Research quality-bias risk assessment

Both reviewers independently assessed the quality of randomized controlled trials in the included studies utilizing the Cochrane Risk of Bias (RoB) 2 methodology. We categorized each experiment into one of three classifications: high risk, low risk, or a concern over the risk of bias. This classification was determined by evaluating five factors: (i) a randomized method; (ii) deviations from intended interventions; (iii) absent outcome data; (iv) outcome measurements; and (v) selection of the reported result.

2.6. Statistical analysis

A meta-analysis was conducted utilizing RevMan 5.4 software. If I^2>50% and P<.1, significant heterogeneity among the studies was observed, necessitating the employment of a random-effects model; conversely, if I^2≤50% and P≥.1, heterogeneity was deemed minimal, warranting the use of a fixed-effects model. The standard mean difference (SMD) or weighted mean difference (WMD) served as the statistical variable for continuous data, while relative risk (RR) was employed as the impact size for dichotomous data, with 95% confidence intervals (95% CI) computed. A two-sided *P*-value <.05 was considered statistically significant. Narrative synthesis was conducted for individual studies or where meta-analysis was not applicable.

2.7. Assessment of evidence quality

The evidence quality was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology by two reviewers. The GRADE assessment evaluated the risk of bias, consistency of results across accessible studies, precision of the results, directness, and the potential for publication bias. The evidence quality was classified as high, moderate, poor, or very low according to the assessments of the outcome.

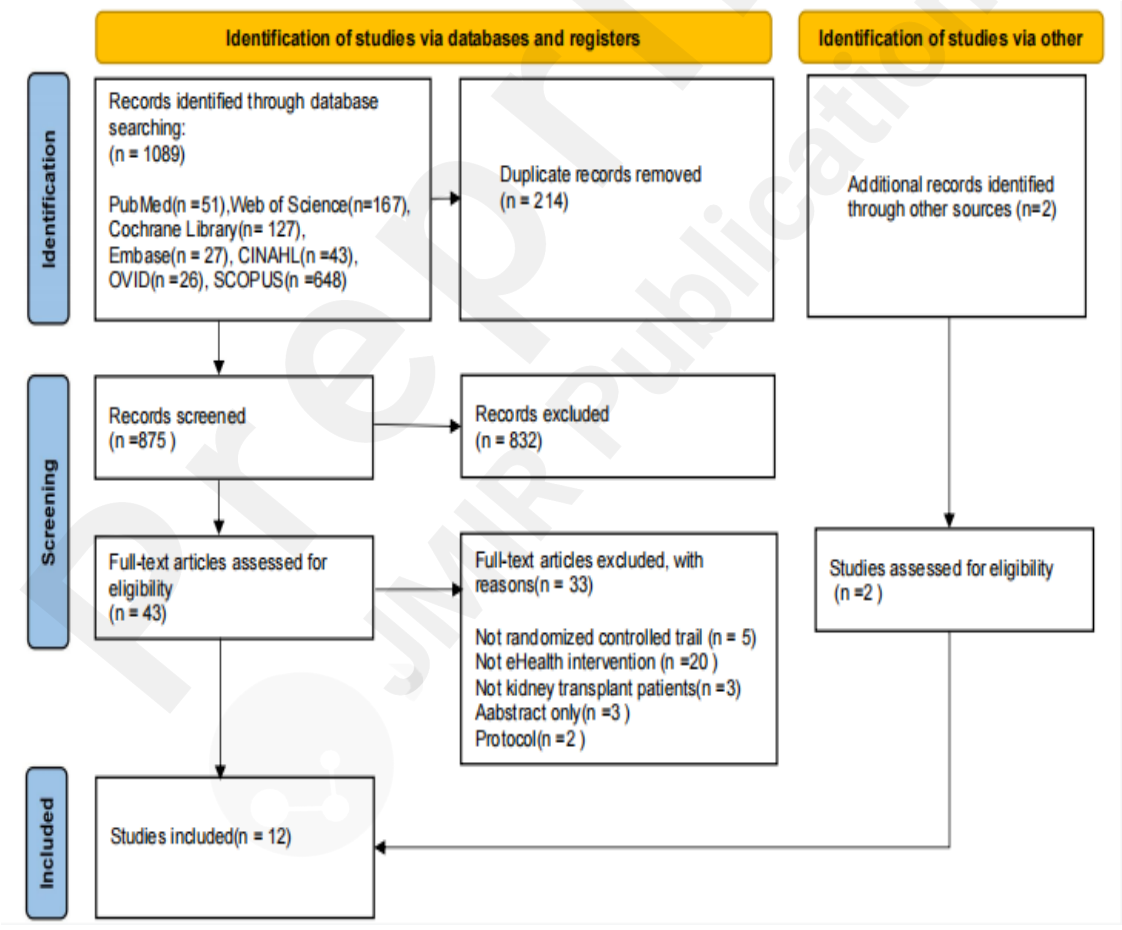


Fig. 1. PRISMA flowchart

Table1. Descriptive summary of included studies.

Study First Author (year,country)	Sample size (n)		Age(mean /median)		Intervention(duration)	Control	Measurement point (months)	Outcomes (measures)
	I	C	I	C				
Erdal et al. (2025,Turkey) [19]	50	50	40.8	42.9	Medication SMS reminders (3 months) Medication reminder text messages are delivered four times per day, with medication educational text messages sent on Mondays, Wednesdays, and Fridays.	No intervention	1,2,3	Medication adherence (1) Objective: tacrolimus blood concentration (2) Subjective: IMAS (self-report questionnaire)
McGillicuddy et al. (2013,USA) [20]	9	10	42.4	57.6	Mobile phone-based medication monitoring (3 months) On the prescribed dosage day and time, the intervention group got customisable reminder signals (light, chime, phone calls, or text messages). They were texted, emailed, or called when medication non-adherence alerts occurred. A weekly email report summarised participants' adherence to physician-prescribed drug dose.	Routine post-transplant care and education	1,2,3	Medication adherence (1) Objective: record electronic pill tray openings using Russell et al.'s adherence score.

Table 1. (Continue)

Study First Author (year,country)	Sample size (n)		Age(mean /median)		Intervention(duration)	Control	Measurement point (months)	Outcomes (measures)
	I	C	I	C				
Fleming et al. (2021,USA) [11]	68	68	50.2	51.2	Mobile phone-based application (12months) The TRANSAFE Rx app tailors the drug regimen to the patient, acting as a medication reminder and providing monthly summary feedback. Summary medication reports are forwarded to the pharmacist for data analysis and prescription changes.	Routine care	Monthly measurements, total 12 months	Medication adherence (1) Objective: Percentage of patients with tacrolimus CV < 40%
McGillicuddy et al. (2020□USA) [8]	41	41	52.1	51.5	Mobile phone-based application (12months) The electronic drug tray will use lights, bells, phone calls, or text messages to remind the patient to take the prescription on the recommended day and time, as well as providing feedback on medication adherence from the previous day. Back-office healthcare providers assess adherence data on a biweekly basis.	Routine post-transplant care and education + Electronic drug trays without reminder	1,3,6	Medication adherence (1) Objective: tacrolimus IPV, Percentage of patients with tacrolimus CV < 40%, electronic monitoring (electronic drug tray compartment openings)

Table 1. (Continue)

Study First Author (year,country)	Sample size (n)		Age(mean /median)		Intervention(duration)	Control	Measurement point (months)	Outcomes (measures)
	I	C	I	C				
Low et al. (2019,Australia) [9]	35	36	53.6	48.4	Drug call reminder (12 months) Bi-weekly face-to-face meetings (medication assessments and consumer-centered videos) and health coaching. + MEMS (An electronic microprocessor on the medicine bottle cap can monitor medication adherence based on bottle opening without a reminder function.)	Standard care + MEMS	3,6,9,12	Medication adherence (1) Objective:electronic monitoring (MEMS monitoring of vial openings) (2) Subjective: BAASIS (self-report questionnaire)
Han et al. (2019，South Korea) [21]	70	66	45.0	43.0	Mobile application-based drug monitoring (6 months) Download the Adhere4U app on patients cellphones, which functions are medication reminders, medication tracking, adherence reporting, immunosuppressant information, educational films, and lab results. + MEMS	Routine care + MEMS	1,3,6	Medication adherence (1) Objective: electronic monitoring (MEMS monitoring of vial openings) (2) Subjective: BAASIS, VAS (self-report questionnaire)

Table 1. (Continue)

Study First Author (year,country)	Sample size (n)		Age(mean /median)		Intervention(duration)	Control	Measurement point (months)	Outcomes (measures)
	I	C	I	C				
Schmid et al. (2017,Germany) [22]	23	23	46.0	51.0	Remote Monitoring System (12 months) Three basic components are (i) initiation of chronic care case management after discharge, (ii) initiation of case management in emerging acute care situations, and (iii) a telemedicine-equipped team consisting of a transplant nurse case manager and two senior transplant physicians (nephrologist and surgeon) capable of remote monitoring and real-time video-screen consultations.	Routine care and education	3,6,12	Medication adherence: A Comprehensive Subjective and Objective Adherence Score (CAS)---- tacrolimus blood concentration + Clinician's report score + BAASIS (self-report questionnaire)
Henriksson et al. (2016,Sweden) [17]	40	40	44.3	45.0	Web-based electronic medication dispenser (EMD) (12 months) EMD reminds patients to take their medication at prescribed times with visual and auditory signals, and send regular adherence reports to patients.	Standard care	10 visits in 1 year (Baseline, days7-14,week4,8,12,16 ,20,24,36,52)	Medication adherence (1) Objective: tacrolimus blood concentration, electronic monitoring (EMD monitoring of vial openings)

Table 1. (Continue)

Study First Author (year,country)	Sample size (n)		Age(mean /median)		Intervention(duration)	Control	Measurement point (months)	Outcomes (measures)
	I	C	I	C				
Mansell et al. (2024Canada) [18]	91	82	52.6	49.4	E-video education (12 months) Participants were required to watch a medication education video (in the hospital or at home), perform electronic self-goal-setting exercises, and sign a contract to take medication as prescribed.	Routine education	3,12	Medication adherence (1) Objective: tacrolimus CV (2) Subjective: BAASIS, VAS (self-report questionnaire)
Reese et al. (2017,USA) [23]	39[a] 40[b]	38	50.0[a] 50.0[b]	49.0	Web-based electronic pill bottle (6 months) Group 1: medication reminders from doctors and wireless pill bottles; Group 2: medication reminders from wireless pill bottles. Throughout the stipulated dose time, all individuals in the intervention group were provided a lit, auditory reminder of the drug container. If medication adherence in Intervention Group 1 falls below 90%, the Study Coordinator and Nephrologist will contact the patients by phone.	Electronic pill bottles with no reminder function, recording only medication adherence data	6	Medication adherence (1) Objective: tacrolimus CV, tacrolimus blood concentration, electronic monitoring (electronic pill bottle openings) (2) Subjective: BAASIS (self-report questionnaire)

Table 1. (Continue)

Study First Author (year,country)	Sample size (n)		Age(mean /median)		Intervention(duration)	Control	Measurement point (months)	Outcomes (measures)
	I	C	I	C				
Jung et al. (2020,South Korea) [10]	51	54	49.9	49.0	Remote monitoring system (6 months) Pill boxes remind patients to take their medications at the right time, and the home monitoring device sends pill box medication data to the EMR for integration and analysis. SMS alerts will notify medical professionals and patients of missed or incorrect doses.	Outpatient follow-up	4w,8w,16w,20w,24w	Medication adherence (1) Objective: tacrolimus CV, tacrolimus blood concentration
Foster et al. (2018,Canada) [24]	81	88	15.5	15.8	Communication-based remote medication reminders (12 months) A quarterly adherence support group of patients, coaches and parent jointly reviews medication adherence data and identifies barriers to use. Allow self-selected medicine reminders by SMS, email, or visual signals. Electronic pill boxes were used to record medication administration in both the control and intervention groups.	3 monthly meetings with a coach who only listens and offers general help	3,6,9,12	Medication adherence (1) Objective: electronic monitoring (electronic pill box openings) (1) Subjective: MAM-MM (self-report questionnaire)

Footnotes:

a= Intervention Group 1, b = Intervention Group 2

CV = Coefficient of Variation, BAASIS= Basel Assessment of Adherence to Immunosuppressive Medication Scale, IMAS = Immunosuppressive Medication Adherence Scale , MAM-MM = Medical Adherence Measure Medication Module, EMR = Electronic Medical Record, VAS = Visual Analog Scale, MEMS = Medication Event Monitoring System, EMD = Electronic Medication Dispenser, SMS = Short Messaging Service, CAS = Composite Adherence Score

3. Results

3.1. Study selection

Our searches initially produced a total of 1089 studies. Following the elimination of 214 duplicate articles, an extra 832 irrelevant articles were excluded based on an evaluation of their titles and abstracts, culminating in a final selection of 43 papers for a comprehensive review. A total of 10 papers were selected for inclusion in the systematic review. By integrating two supplementary articles sourced from different references, the total number of studies included in the study reached 12 (Fig. 1).

3.2. Characteristics of included studies

3.2.1. Intervention characteristics.

Table 1 shows the characteristics of the interventions used in the twelve studies included in this analysis. These interventions include medication SMS reminders [19], mobile phone-based medication monitoring [20], mobile phone-based applications [8,11,19], drug call reminders [9], remote monitoring systems [10,22], wireless electronic pillboxes [17,23], e-video education [18], and remote alerts based on communication technology [24].

The specifics of the intervention for each study are as follows.In Erdal et al.'s [19] study, the intervention group received immunosuppressant drug reminders four times a day and drug education text messages on Mondays, Wednesdays, and Fridays for three months. In McGillicuddy et al.'s [20] study, on the prescribed dosage day and time, the intervention group got customized reminder signals (lights, chimes, phone calls, or text messages). When medication non-adherence alerts occurred, they received texts, emails, or calls. A weekly email report summarized participants' adherence to doctor-prescribed drug doses. In Fleming et al.’s [11] study, intervention group participants receive personalized prescription regimens, medication reminders, and monthly summary comments from the self-developed TRANSAFE Rx app. Pharmacists analyze and change medication according to summary reports. In McGillicuddy et al.’s [8] study, the electronic drug tray will use lights, bells, phone calls, or text messages to remind the intervention group to take their prescriptions on time and provide medication adherence data from the previous day. Back-office healthcare providers evaluate adherence biweekly. In Low et al.'s [9] study, biweekly face-to-face meetings (medication assessments and consumer-centered videos) and telephone health coaching for patients in the intervention group were conducted. In Han et al.'s [21] study, download the Adhere4U app on intervention group patients' phones for medication reminders, tracking, adherence reports, immunosuppressant information, educational films, and lab results. In Schmid et al.'s [22] study, at discharge, the intervention group started chronic care chart management, and transplant nurses regularly assessed medication intake through online questionnaires, video screen counseling, and telephone calls to provide timely feedback to transplant physicians in response to unexpected emergencies. In Henriksson et al.'s [17] study, the electronic medication dispenser reminds the intervention group to take their medication at prescribed times with visual and auditory signals and sends regular adherence reports to patients. In Mansell et al.'s [18] study, intervention group participants were required to watch the medication education video complete self-goal-setting exercise activities on an electronic device and sign a contract to take medication as prescribed by their doctor. In Reese et al.'s [23] study, intervention groups 1 and 2, the smart pillbox will flash and beep to remind participants to take their medication. If Intervention Group 1 patients have less than 90% medication adherence (measured every two weeks), the study coordinator and nephrologist will call them. In Jung et al.'s [10] study, pill boxes remind the intervention group to take their medications at the right time, and the home monitoring device sends pillbox medication data to the EMR for integration and analysis. SMS alerts will notify medical professionals and patients of missed or incorrect doses. In Foster et al.'s [24] study, a medication adherence support group, consisting of patients, coaches (specially trained clinical investigators), and parents, convenes quarterly to analyze adherence data and identify obstacles to medication utilization. Patients are permitted to select their preferred medicine reminders through text message, email, or visual cues.

3.2.2. Outcomes

The dependent variable was medication adherence, and the twelve studies incorporated in this analysis showed considerable variation in the assessments of medication adherence. Each study defined medication adherence as follows. Erdal et al. [19] assessed medication adherence using the Immunosuppressive Medication Adherence Scale (IMAS) self-adherence evaluation (continuous data) and tacrolimus blood concentrations (dichotomized data). The 11-item self-report IMAS assesses immunosuppressive medicine adherence. Eight items are rated on a five-point Likert scale from ‘never, rarely, sometimes, often, and always.’ Yes or no for the remaining three questions. Higher item scores promote medication adherence. Total scores are 11-55 and come from item scores. Scale Cronbach's alpha 0.61. Patient tacrolimus blood levels were measured 12 hours following medication. The mean tacrolimus plasma concentration was estimated from blood samples at months 1, 2, and 3 post-intervention. This study defined ‘medication nonadherence’ as a tacrolimus level <5 from >10 ng/mL.

McGillicuddy et al. [20] objectively measured medication time using Russell et al.'s adherence score. Medication adherence was taking immunosuppressants within three hours of the dose. Doses taken within three hours received a full score, those within six hours received a half score, and missing doses received zero points. Participants received daily scores from 0.0 to 1.0, which were averaged over the month.

Fleming et al. [11] investigated medication adherence employing two objective physiologic indicators: tacrolimus IPV and the percentage of patients with an IPV <40%. Tacrolimus IPV was measured using the coefficient of variation (CV) ([mean/SD]·100) at monthly intervals for each patient (12-month rolling average), beginning with randomization and lasting 12 months. Rolling averages were calculated and estimated at monthly intervals. Each month, one month's worth of tacrolimus levels was added to the CV calculation, while the preceding month's levels were removed. In this article, a narrative synthesis of the two outcomes was conducted. In a 2020 study by McGillicuddy et al. [8], the Russell et al. adherence score (dichotomized data) was used to objectively assess patient adherence to medication using tacrolimus IPV, the percentage of patients with tacrolimus IPV <40%, and medication administration data monitored by an electronic medication tray.

The study by Han et al. [21] investigated medication adherence via the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) and Visual Analog Scale (VAS) (dichotomized data), as well as the objective method MEMS V prescription container lids (dichotomized data). Four items on the BAASIS examine medication dosage, duration, holidays, and tapering on a 6-point scale from “never” (0 points) to “every day” (5 points). VAS values range from 0 (never take medication as prescribed) to 100 (always take medication as prescribed). The BAASIS classified noncompliance as a score ≥1 on any of the four categories, while the VAS defined it as a score below 100. Our study used values measured by BAASIS. The objective findings were binary indicators of 6-month cumulative adherence based on electronic monitoring (MEMS) data. Medication nonadherence was defined as adherence <98%, >102%, or at least one medication holiday. The top limit of 102% relates to repeated overdosing, while medication holidays are durations without drug ingestion >3 times the normal interval. Low et al. [9] also took the BAASIS and MEMS V prescription container lids to assess medication adherence. Patients with ≥97% ‘taking adherence’ and ‘timing adherence’ were considered adherent. Taking adherence is the proportion of days with the correct number of MEMS openings divided by the total monitored days. Timing adherence is the percentage of days the MEMS opened within 2 hours of the patient's average time.

In Schmid et al. 's study [22], nonadherence was measured with a composite adherence score, which included a self-report, two clinician reports, and a tacrolimus test report. The nonadherence was determined using the Composite Adherence Score (CAS) threshold system defined by Schäfer-Keller et al. [25]. To better understand

the dynamics of nonadherence, they changed the CAS percentage grading into an interval grading system and a description of nonadherence. Assessed at baseline, post-intervention months 3, 6, and 12.

Henriksson et al. [17] employed objective markers to assess medication adherence, such as using an electronic dispenser to track whether patients took their prescribed medication on time and measuring tacrolimus levels. Mansell et al. [18] assessed medication adherence using subjective and objective measures like the BAASIS scale (dichotomized data), VAS, and tacrolimus IPV. This review used BAASIS and tacrolimus IPV results. Reese et al. [23] used two types of measurements to investigate medication adherence: objective data from electronic pill bottles, tacrolimus blood concentration, and tacrolimus IPV (continuous data) and subjective data from the BAASIS self-rated adherence scale (dichotomized data). Medication adherence was determined by the number of days when the bottle was opened at the appropriate time for daily tacrolimus dosages, tacrolimus blood concentrations, and BAASIS scores using a validated 5-item self-report questionnaire intended for immunosuppression.

Jung et al. [10] conducted their study using a variety of objective metrics. For example, tacrolimus blood levels (continuous data), tacrolimus IPV (continuous data), and electronic pillboxes were utilized to record medication adherence data, such as dose-taking adherence, dose-frequency adherence, dose-interval adherence, and drug holidays. Dose adherence was computed as (number of pills ingested during a specified timeframe/number of pills prescribed within the same timeframe)× 100%. Dose-frequency adherence was determined by the formula (number of days with accurate daily dosage in a specified time frame/number of days within the same time frame). Dosing interval adherence was determined by the formula (number of days with accurate dosing intervals within a certain time frame/number of days in the same time frame) × 100%. A range of ± 25% was employed to delineate the appropriate dosing interval. In their research, the medication was administered bi-daily with a 12-hour dose interval. The acceptable dose interval range is 9 to 15 hours. Drug holidays were calculated as (days not taken / number of days in the same time) multiplied by 100%.

In Foster et al.’s [24] study, the main outcomes were electronically recorded 'taking' adherence (the percentage of prescribed doses of immunosuppressive medications consumed) and 'timing' adherence (the percentage of doses of immunosuppressive medications taken within 1 hour before and 2 hours after the scheduled administration time) on each observation day. Secondary outcomes include the Medical Adherence Measure Medication Module (MAM-MM) self-reported adherence (continuous data) [26]. The MAM-MM measured self-reported taking and timing adherence by counting doses taken in the previous week and 2 hours after the suggested time. Each patient's MAM-MM score averaged four post-intervention months (3, 6, 9, and 12). This review used the MAM-MM self-assessment and e-measurement outcomes.

3.3. Risk of bias in included studies

To evaluate the risk of bias in each study, we used the updated Cochrane Risk of Bias instrument for randomized trials (RoB 2.0). Figures S1 and S2 summarize the risk-of-bias evaluations for the included studies. Eleven studies were assessed as having ‘some concerns,’ while one was deemed to have ‘high risk.’ Six studies failed to disclose allocation concealment details [8,10,11,20,23,24], while four of them merely indicated "randomized allocation" without more elaboration [8,11,20,23]. Because of the unique nature of eHealth, blinding recipients and intervention implementers is challenging, which may have an impact on the intended intervention. No missing outcome data. One study [22], which was not blinded to the assessor, measured medication adherence using CAS, which consisted of a patient self-report, two clinician reports, and a report of a tacrolimus test, and the assessor (clinician) was aware of subgroups that could have affected the effectiveness of the intervention, and thus rated it as ‘high-risk.’ In other studies, outcome measures consisted of subjective

self-reports or objective data (electronic monitoring, biochemical indicators) supplied by patients, with minimal assessor influence. No option existed for reporting outcome bias. Overall, the quality rating evaluated by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology was deemed low (Table S3). Publication bias could not be assessed because of the limited number of trials.

3.4. Effects of interventions

All twelve studies assessed medication adherence among kidney transplant recipients following an eHealth intervention. The analysis comprised 897 participants. The measured data were taken at least three months after the initiation of the intervention. Two studies used values measured at three months [19,20], four at six months [8,10,21,23], and six at twelve months [9,11,17,18,22,24].

Measures of medication adherence can be classified as subjective or objective. In six studies [9,18,19,21,23,24], medication adherence was evaluated subjectively by self-reported data. The objective assessments of medication adherence comprised 8 studies utilizing electronic monitoring [8-10,17,20-24], 4 studies measuring tacrolimus blood concentrations [10,17,19,23], 5 studies analyzing tacrolimus coefficients of variation [8,10,11,18,23], and 2 studies evaluating the percentage of patients with <40% adherence [8,11]. A separate study [22] utilized a thorough evaluation comprising both subjective and objective elements. A meta-analysis was conducted for both dichotomous and continuous data, while a narrative synthesis was employed for individual studies or in instances where meta-analysis was not applicable.

3.4.1. Medication adherence assessed by self-report

A total of 6 studies used self-report assessment questionnaires [9,18,19,21-24]. Four studies reported adherence to medication as assessed by BAASIS [9,18,21,23], and three studies provided analyzable data with statistical heterogeneity of 11% and a P=.34, so a fixed effects model was used [18,21,23]. The results showed no difference between the two groups (RR=0.98, 95% CI [0.85, 1.13], Z=0.34, P=.73) (Fig. 2A). One study [9] did not provide specific values and thus was not included in the meta-analysis. However, it showed that the proportion of people in the control group who were compliant with their medication decreased significantly from baseline to 3 to 12 months (P<.001), while the proportion of people in the intervention group who were compliant with their medication remained stable throughout the period. The other two studies [19,24] offered continuous data for self-adherence evaluation, and SMD and random effects models were utilized due to the use of different assessment methods, with statistical heterogeneity of 59% and P=.09. According to the findings, the eHealth intervention significantly increased patients' medication adherence (SMD=0.38, 95% CI [0.07, 0.68], Z=2.43, P=.01), as shown in Figure 2(B).

3.4.2. Medication adherence monitored by electronic devices

Eight studies reported medication adherence monitored by electronic devices [8-10,17,20-24], three of which offered dichotomous data with 53% statistical heterogeneity and P=.09 [8,21,23], so a random effects model was applied. The results demonstrated that the eHealth intervention increased patients' medication adherence with a statistically significant difference (RR = 1.46, 95% CI [1.11, 1.90], Z = 2.75, P=.006) (Figure 3A). One study [20] with continuous data showed a significant difference between the two groups (MD=0.37, 95% CI [0.27, 0.47], Z=7.34, P<.001) (Figure 3B). Meta-analysis was not applied to the remaining four studies [9,10,17,24], which were synthesized narratively separately. The Low et al.'s [9] study did not provide quantitative values, yet it assessed that the effect was comparable between the two groups. In the study by Henriksson et al. [17], medication adherence in the intervention group was reported at 97.8%, while the control group was not monitored (electronic medication dispensers that could record the number of times the medication was taken were not issued). In the Jung et al. Study [10], dose-taking adherence was >98% in both groups, and there were no significant differences in dose-frequency adherence, dose-interval adherence, or medication holidays. In the Foster et al. Study [24], during the intervention period, on 78% of days, intervention participants had 100% of taking adherence compared to 68% in the control group. Intervention participants were significantly more likely to take adherence better than controls (OR=1.66, 95% CI [1.15, 2.39], P=.006).

And intervention participants had 100% timing adherence on 73% of days during the intervention interval and had substantially higher chances of higher timing adherence ratings (OR=1.74, 95% CI [1.21, 2.50], *P*=.003) than controls, who had 100% timing adherence on 61% of days.

3.4.3. Tacrolimus blood levels

Four studies reported tacrolimus blood concentrations [10,17,19,23]. Two studies [10,23] provided continuous data with a statistical heterogeneity of 1% and a *P*=.37, so a fixed effects model was used. The results showed no statistical difference between the two groups (MD=0.15, 95% CI [-0.21, 0.51], Z=0.83, *P*=.41), as shown in Figure 4(A). One study [19] using dichotomized data found a significant difference between the two groups (RR=1.38, 95% CI [1.04, 1.82], Z=2.27, *P*=.02) (Figure 4B). Another study [17] did not give analyzable data but did show that the difference between the two groups was not statistically significant.

3.4.4. Tacrolimus IPV

Five studies gave tacrolimus IPV [8,10,11,18,23], and two studies [10,23] provided continuous data with 0% statistical heterogeneity and a *P*=.82, so a fixed effects model was applied. There was no statistical difference between the two groups [MD=-0.02, 95% CI (-0.07, 0.03), Z=0.83, *P*=.40], as shown in Figure 5. The study by Fleming et al. [11] did not provide meta-analyzable data. However, it asserted that the tacrolimus IPV at 12 months was significantly lower in the intervention group and statistically distinct from the control group (*P*=.0133). This aligns with the findings of McGillicuddy et al. [8] (*P*=.046). The study by Mansell et al. [18] demonstrated that tacrolimus IPV did not exhibit a statistically significant difference between the two groups, with the 95% confidence interval for the change in slope ranging from -0.018 to 0.071.

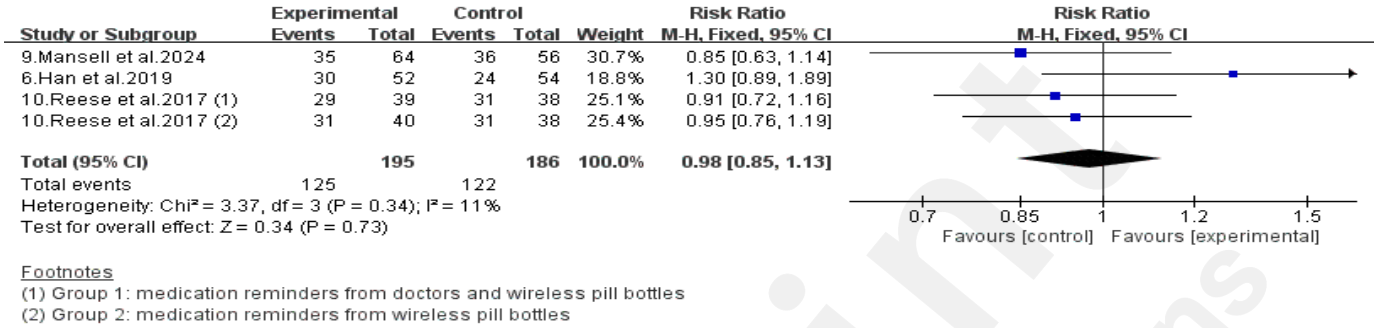
3.4.5. Proportion of patients with tacrolimus CV <40%

Narrative synthesis of two studies [8,11]. Fleming et al. [11] conducted a 12-month randomized controlled trial of 136 KT recipients and found that the control group had a higher proportion of recipients with a tacrolimus CV <40% at baseline (*P*=.017), but the difference between the two groups at 12 months was not statistically significant (*P*=.224). However, the value of the tacrolimus CV <30% after 12 months was substantially different between the two groups, with the intervention group over-representing in reaching this indicator (*P*=.033), and the baseline of the two groups was comparable (*P*=.765). McGillicuddy et al. [8] showed that more recipients in the intervention group obtained a tacrolimus CV < 40% following a 6-month randomized controlled trial (80% versus 70%, *P*=.001).

3.4.6. Comprehensive scoring of medication adherence

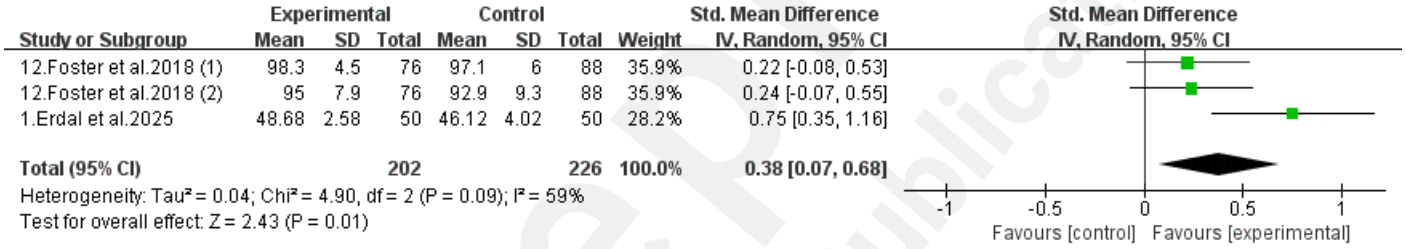
In the study by Schmid et al. [22], nonadherence was measured by a CAS, which included a self-report, two clinician reports, and a tacrolimus test report. Their 12-month randomized controlled trial of 46 kidney transplant patients found that the intervention group had a lower rate of medication nonadherence compared to the control group (OR=1.90, 95% CI [1.15, 3.14], Z=2.50, *P*=.01), see Figure 6.

(A)



Footnotes
(1) Group 1: medication reminders from doctors and wireless pill bottles
(2) Group 2: medication reminders from wireless pill bottles

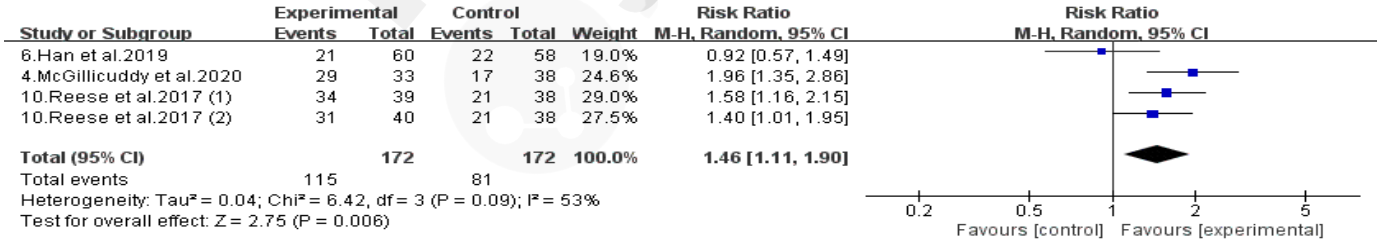
(B)



Footnotes
(1) Taking adherence
(2) Timing adherence

Fig. 2 Medication adherence assessed by self-report: (A) dichotomized data, (B) continuous data.

(A)



Footnotes
(1) Group 1: medication reminders from doctors and wireless pill bottles
(2) Group 2: medication reminders from wireless pill bottles

(B)

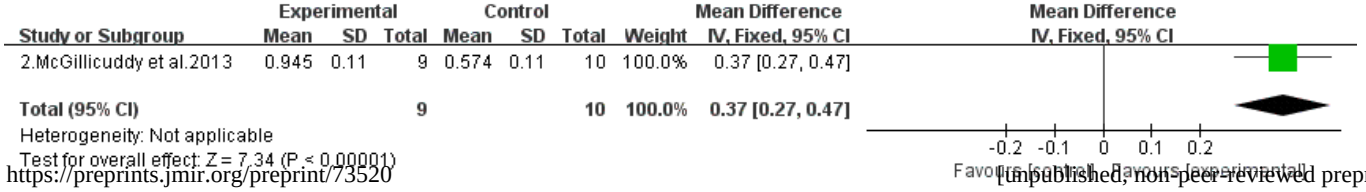
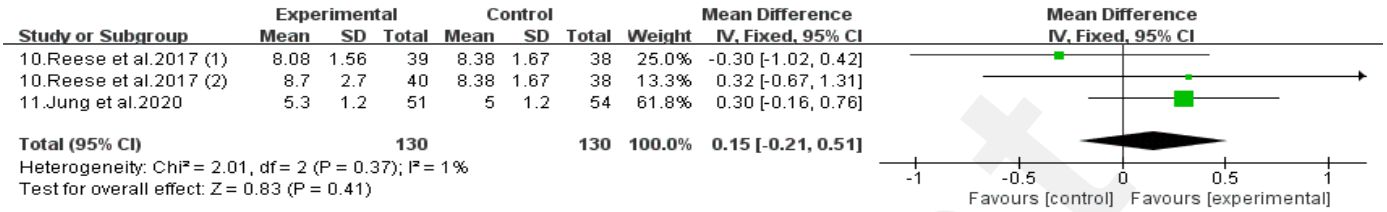


Fig. 3 Medication adherence monitored by electronic devices: (A) dichotomized data, (B) continuous data.

(A)



Footnotes
(1) Group 1: medication reminders from doctors and wireless pill bottles
(2) Group 2: medication reminders from wireless pill bottles

(B)

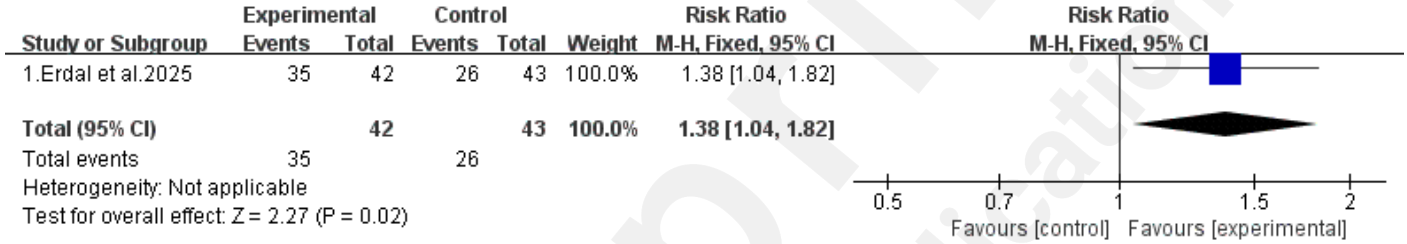
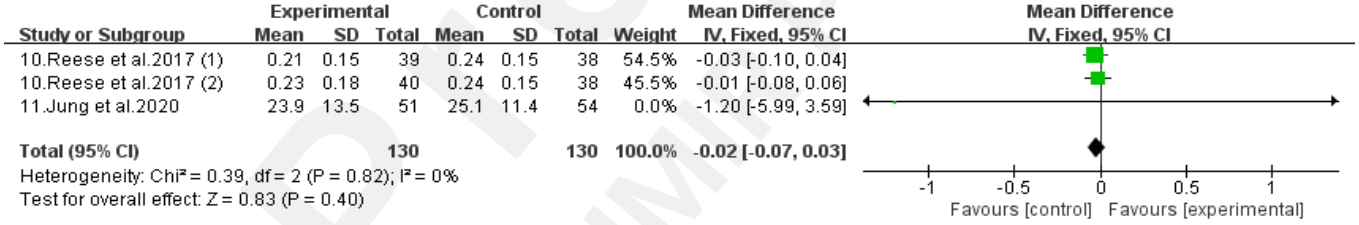


Fig. 4 Tacrolimus Blood Concentration: (A) continuous data, (B) dichotomized data.



Footnotes
(1) Group 1: medication reminders from doctors and wireless pill bottles
(2) Group 2: medication reminders from wireless pill bottles

Fig. 5 Intra-patient variability of tacrolimus concentrations.

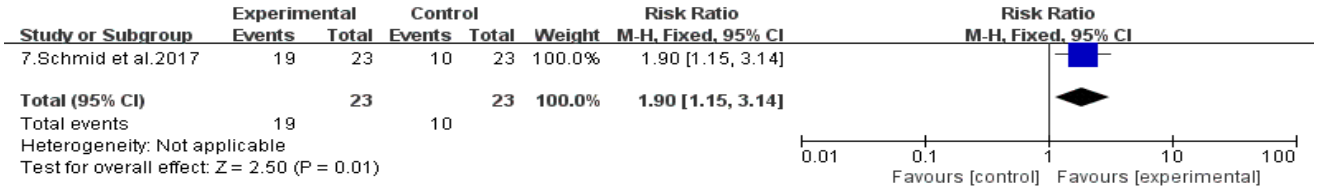


Fig. 6 Comprehensive scoring of medication adherence.

4. Discussion

Genreal Findings

This review investigated the effectiveness of eHealth interventions in improving medication adherence in kidney transplant recipients. Overall, the results were mixed and no definite conclusion could be drawn.

Overview

The 12 randomised controlled trials included in this review produced low-quality evidence, with significant variation in assessment methods and data sources. Measures were classified as objective and subjective medication adherence, while data types were divided into binary and continuous data, resulting in constraints on aggregating the 12 research. Consequently, subgroup analyses were conducted by categorising objective and subjective indicators, along with dichotomous and continuous data. Furthermore, a narrative synthesis was employed for single studies and those unsuitable for meta-analysis.

The effectiveness of eHealth interventions in improving medication adherence in renal transplant recipients was mixed, as evidenced by the overall outcomes of self-reported and electronic monitoring assessments. Previous meta-analyses indicated significant impacts of eHealth interventions for chronic illnesses such as hypertension (effect size: 0.41, P=.04) and diabetes (effect size: 0.501, P<.001) [27,28], which contradicts the conclusions of this study. It could be related to the fact that the individual trials in this study resulted in a non-significant analysis of the effect; therefore, the results should be regarded with caution, and the relevant confounders clarified.

Implementation challenges and recommendations

Inconsistent effects of eHealth interventions assessed in different ways. Four trials found no significant effect with self-reported medication adherence assessments [18,21,23,24]. Three trials found no significant effect of electronic monitoring on drug adherence [9,10,21]. Reading through the full text above revealed certain reasons for our negative results.

Low utilization

Low utilization of electronic devices may have affected the true effectiveness of eHealth interventions. Han et al. [21] discovered that 50% of patients discontinued using Adhere4U during the first month of the intervention, and only 10% remained on it at the end of the research. Mansell et al. [18] found that merely 69% of 173 participants complied with viewing electronic video education. In the Low et al.’s research [9], less than 40% of individuals adhered to MEMS, and the rate was considerably lower among men with living kidney transplants and no dialysis history. This is consistent with earlier studies on risk variables related to non-adherence to use [29,30]. However, low utilization of electronic devices may also be due to study fatigue. Previous studies have shown a 72.8% incidence of polypharmacy in kidney transplant recipients [31], which, combined with the daily electronic monitoring required, adds to the burden of medication administration, which involves medication management assistance for patients. In addition, the high attrition factors identified in this study also included the ease of deleting the medication reminder settings, lack of feedback from clinicians, and the fact that participants had formed established medication habits [21], which has also been confirmed in previous studies [32]. This reminds us of the need to assess the length of postoperative transplantation, the number of

medications, and the psychological burden of the participants when selecting study participants to reduce the risk of participants having difficulty in accepting new methods.

Intentional nonadherence

An alternative explanation for our negative results is that participants' intentional nonadherence may be more prevalent than unintentional nonadherence. This study found that participants were less likely to be non-adherent to their medication due to forgetfulness, as there were regular reminders by email or phone. Previous research indicates that noncompliance with immunosuppression in kidney transplant recipients is primarily unintentional [33,34], with forgetfulness and disruption of everyday life recognised as major causes [35]. However, both intentional and unintentional noncompliance can only be measured by self-report, which is inherently biased by socially expected answers. If intentional nonadherence is more common than we realise, eHealth interventions will not have the predicted positive impact on nonadherence rates. Second, electronic monitoring devices cannot ensure that patients swallow the pill or take the correct dose each time they open the pill box. As a result, it is recommended that a comprehensive approach be taken to assess patients' medication adherence, such as combining self-reporting, electronic monitoring devices, and tacrolimus blood levels [36].

The ceiling effect

The ceiling effect may have affected the significance of the results. Jung et al. [10] showed that an information communication-based centralized monitoring system did not improve medication adherence in kidney transplant recipients due to high baseline adherence (99%-100%). This is consistent with the findings of Low et al. [9] and Foster et al. [24]. Previous studies have avoided this by delivering interventions to nonadherent patients after baseline assessments [37]. Future studies should consider using baseline screening to firstly ensure that devices assessing the primary outcome can be successfully implemented in patient cohorts and secondly for the exclusion of highly adherent patients.

Reflections and Outlook

Previous systematic reviews have examined various interventions and assessed their impact on improving medication adherence in organ transplant recipients [37-39]. Most of the studies in these systematic reviews demonstrated that the interventions were effective. These findings should be considered in conjunction with the above confounding factors that influenced the results of this study, suggesting that the true effects of eHealth interventions are still promising for the future. Given that kidney transplant recipients require long-term medication, as do patients with cardiovascular disease or diabetes [27,28], this suggests the potential value of studying eHealth interventions for medication adherence in kidney transplant recipients. Furthermore, the swift advancement of communication and information technology, coupled with the rising number of mobile phone and Internet users, enhances the probability of employing eHealth interventions in the future, rendering our study both timely and relevant.

The findings of this study do not yet clarify the efficacy of the eHealth intervention in improving tacrolimus blood levels and tacrolimus IPV in kidney transplant recipients, and more prospective studies are required to validate this. Previous studies have found that tacrolimus IPV is substantially related to nonadherence and that high tacrolimus IPV increases the likelihood of distant graft rejection and loss [40,41]. Previous researchers enhanced patient adherence to medicine by optimising the tacrolimus regimen, which involved switching patients from twice-daily tacrolimus to a once-daily tacrolimus extended-release dose form [42,43].This method has had different degrees of success. However, nonadherence is a dynamic, complex issue that is best addressed with multidimensional interventions. In the digital age, multidimensional interventions to improve noncompliance are increasingly reliant on mobile technology. The eHealth interventions used in this study included education, self-monitoring, reminders, medical staff monitoring, and timely information exchange between doctors and patients, potentially leading to more personalised, precise, and convenient drug therapy services for patients. Compared to traditional treatment, eHealth breaks down time and space boundaries and lowers medical labour costs, particularly during Covid-19.

5.Limitations

The limited number of included studies and the low GRADE quality score necessitate cautious interpretation of the results. Second, we only included studies from database searches and did not search the grey literature. Third, the lack of blinding and allocation concealment in some of the studies may have led to bias against the results, but due to the specific nature of eHealth interventions, it is difficult to blind patients or interveners. Fourth, when selecting immunosuppressant outcomes, we only selected tacrolimus because it was the most commonly used drug, taking into account post-transplant medication adjustments. Fifth, some articles did not provide specific data, which were presented as graphs or text and could not be analyzed meta-analytically. Sixth, due to the limited number of trials, it was not possible to generate a funnel plot, so we could not determine publication bias. However, it is expected to be low considering that there have been trials that have published negative results.

6.Conclusion

In conclusion, we did not find a significant effect of eHealth interventions in improving medication adherence in kidney transplant recipients. Our evidence is limited by multiple confounding factors. Despite the negative nature of our results, eHealth remains an attractive tool for improving patient medication adherence. More high-quality studies are needed in the future to further optimize eHealth intervention strategies. During which attention needs to be paid to baseline screening, study participant selection, measurement methods, and assessment of technical feasibility.

Acknowledgements

This research got no specific funding from any public, commercial, or non-profit source.

Conflict of interest

There is no conflict of interest amongst the authors of this paper.

Funding

No funding.

Abbreviations

CV: Coefficient of Variation
IPV: Intra-patient Variability
BAASIS: Basel Assessment of Adherence to Immunosuppressive Medication Scale
IMAS: Immunosuppressive Medication Adherence Scale
MAM-MM: Medical Adherence Measure Medication Module
EMR: Electronic Medical Record
VAS: Visual Analog Scale
MEMS: Medication Event Monitoring System,
EMD: Electronic Medication Dispenser
SMS: Short Messaging Service
CAS: Composite Adherence Score
WHO: World Health Organisation
GODT: Global Observatory for Organ Donation and Transplantation

References

1. WHO-ONT. (2023). INTERNATIONAL REPORT ON ORGAN DONATION AND TRANSPLANTATION ACTIVITIES [online] Available at : <www.organdonationalliance.org> [Accessed 05 February 2025]
2. de Weerd, A. E., & Betjes, M. G. H. (2018). ABO-Incompatible Kidney Transplant Outcomes: A Meta-Analysis. *Clin J*

Am Soc Nephrol, *13*(8), 1234-1243. https://doi.org/10.2215/cjn.00540118

3. Poggio, E. D., Augustine, J. J., Arrigain, S., Brennan, D. C., & Schold, J. D. (2021). Long-term kidney transplant graft survival-Making progress when most needed. *Am J Transplant*, *21*(8), 2824-2832. https://doi.org/10.1111/ajt.16463

4. Singh, N., Samant, H., Hawxby, A., & Samaniego, M. D. (2019). Biomarkers of rejection in kidney transplantation. *Curr Opin Organ Transplant*, *24*(1), 103-110. https://doi.org/10.1097/mot.0000000000000606

5. Wang, W., Teng, Y., Xue, J. J., Cai, H. K., Pan, Y. B., Ye, X. N., Mao, X. L., & Li, S. W. (2022). Nanotechnology in Kidney and Islet Transplantation: An Ongoing, Promising Field. *Front Immunol*, *13*, 846032. https://doi.org/10.3389/fimmu.2022.846032

6. Mathes, T., Großpietsch, K., Neugebauer, E. A. M., & Pieper, D. (2017). Interventions to increase adherence in patients taking immunosuppressive drugs after kidney transplantation: a systematic review of controlled trials. *Syst Rev*, *6*(1), 236. https://doi.org/10.1186/s13643-017-0633-1

7. Tang, J., James, L., Howell, M., Tong, A., & Wong, G. (2020). eHealth Interventions for Solid Organ Transplant Recipients: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Transplantation*, *104*(8), e224–e235. https://doi.org/10.1097/TP.0000000000003294

8. McGillicuddy, J. W., Chandler, J. L., Sox, L. R., & Taber, D. J. (2020). Exploratory Analysis of the Impact of an mHealth Medication Adherence Intervention on Tacrolimus Trough Concentration Variability: Post Hoc Results of a Randomized Controlled Trial. *Ann Pharmacother*, *54*(12), 1185-1193. https://doi.org/10.1177/1060028020931806

9. Low, J. K., Manias, E., Crawford, K., Walker, R., Mulley, W. R., Toussaint, N. D., Dooley, M., Kennedy, E., Smith, C. L., Nalder, M., Yip, D., & Williams, A. (2019). Improving medication adherence in adult kidney transplantation (IMAKT): A pilot randomised controlled trial. *Sci Rep*, *9*(1), 7734. https://doi.org/10.1038/s41598-019-44002-y

10. Jung, H. Y., Jeon, Y., Seong, S. J., Seo, J. J., Choi, J. Y., Cho, J. H., Park, S. H., Kim, C. D., Yoon, Y. R., Yoon, S. H., Lee, J. S., & Kim, Y. L. (2020). ICT-based adherence monitoring in kidney transplant recipients: a randomized controlled trial. *BMC Med Inform Decis Mak*, *20*(1), 105. https://doi.org/10.1186/s12911-020-01146-6

11. Fleming, J. N., Gebregziabher, M., Posadas, A., Su, Z., McGillicuddy, J. W., & Taber, D. J. (2021). Impact of a pharmacist-led, mHealth-based intervention on tacrolimus trough variability in kidney transplant recipients: A report from the TRANSAFE Rx randomized controlled trial. *Am J Health Syst Pharm*, *78*(14), 1287-1293. https://doi.org/10.1093/ajhp/zxab157

12. Miao, Y., Luo, Y., Zhao, Y., Liu, M., Wang, H., & Wu, Y. (2024). Effectiveness of eHealth Interventions in Improving Medication Adherence Among Patients With Cardiovascular Disease: Systematic Review and Meta-Analysis. *J Med Internet Res*, *26*, e58013. https://doi.org/10.2196/58013

13. Zeng, Z., Wu, T., Lv, M., Qian, J., Chen, M., Fang, Z., Jiang, S., & Zhang, J. (2022). Impact of mobile health and telehealth technology on medication adherence of stroke patients: a systematic review and meta-analysis of randomized controlled trials. *Int J Clin Pharm*, *44*(1), 4-14. https://doi.org/10.1007/s11096-021-01351-x

14. Gandolfini, I., Palmisano, A., Fiaccadori, E., Cravedi, P., & Maggiore, U. (2022). Detecting, preventing and treating non-adherence to immunosuppression after kidney transplantation. *Clin Kidney J*, *15*(7), 1253-1274. https://doi.org/10.1093/ckj/sfac017

15. Kuypers, D. R. J. (2020). From Nonadherence to Adherence. *Transplantation*, *104*(7), 1330-1340. https://doi.org/10.1097/tp.0000000000003112

16. Belaiche, S., Décaudin, B., Dharancy, S., Noel, C., Odou, P., & Hazzan, M. (2017). Factors relevant to medication non-adherence in kidney transplant: a systematic review. *Int J Clin Pharm*, *39*(3), 582-593. https://doi.org/10.1007/s11096-017-0436-4

17. Henriksson, J., Tydén, G., Höijer, J., & Wadström, J. (2016). A Prospective Randomized Trial on the Effect of Using an Electronic Monitoring Drug Dispensing Device to Improve Adherence and Compliance. *Transplantation*, *100*(1), 203-209. https://doi.org/10.1097/tp.0000000000000971

18. Mansell, H., Rosaasen, N., Wichart, J., West-Thielke, P., Blackburn, D., Liu, J., Mainra, R., Shoker, A., Groot, B., Wen, K., Wong, A., Bateni, B., Luo, C., & Trivedi, P. (2024). Video Education and Behavior Contract to Improve Outcomes After Renal Transplantation (VECTOR): A Randomized Controlled Trial. *Patient Prefer Adherence*, *18*, 1589-1602. https://doi.org/10.2147/ppa.S467142

19. Erdal, K., & Karazeybek, E. (2025). Impact of text message reminders on immunosuppressive medication adherence among kidney transplant recipients: A randomized controlled study. *J Eval Clin Pract*, *31*(1), e14178.

https://doi.org/10.1111/jep.14178
20. McGillicuddy, J. W., Gregoski, M. J., Weiland, A. K., Rock, R. A., Brunner-Jackson, B. M., Patel, S. K., Thomas, B. S., Taber, D. J., Chavin, K. D., Baliga, P. K., & Treiber, F. A. (2013). Mobile Health Medication Adherence and Blood Pressure Control in Renal Transplant Recipients: A Proof-of-Concept Randomized Controlled Trial. *JMIR Res Protoc*, *2*(2), e32. https://doi.org/10.2196/resprot.2633
21. Han, A., Min, S. I., Ahn, S., Min, S. K., Hong, H. J., Han, N., Kim, Y. S., Ahn, C., & Ha, J. (2019). Mobile medication manager application to improve adherence with immunosuppressive therapy in renal transplant recipients: A randomized controlled trial. *PLoS One*, *14*(11), e0224595. https://doi.org/10.1371/journal.pone.0224595
22. Schmid, A., Hils, S., Kramer-Zucker, A., Bogatyreva, L., Hauschke, D., De Geest, S., & Pisarski, P. (2017). Telemedically Supported Case Management of Living-Donor Renal Transplant Recipients to Optimize Routine Evidence-Based Aftercare: A Single-Center Randomized Controlled Trial. *Am J Transplant*, *17*(6), 1594-1605. https://doi.org/10.1111/ajt.14138
23. Reese, P. P., Bloom, R. D., Trofe-Clark, J., Mussell, A., Leidy, D., Levsky, S., Zhu, J., Yang, L., Wang, W., Troxel, A., Feldman, H. I., & Volpp, K. (2017). Automated Reminders and Physician Notification to Promote Immunosuppression Adherence Among Kidney Transplant Recipients: A Randomized Trial. *Am J Kidney Dis*, *69*(3), 400-409. https://doi.org/10.1053/j.ajkd.2016.10.017
24. Foster, B. J., Pai, A. L. H., Zelikovsky, N., Amaral, S., Bell, L., Dharnidharka, V. R., Hebert, D., Holly, C., Knauper, B., Matsell, D., Phan, V., Rogers, R., Smith, J. M., Zhao, H., & Furth, S. L. (2018). A Randomized Trial of a Multicomponent Intervention to Promote Medication Adherence: The Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial (TAKE-IT). *Am J Kidney Dis*, *72*(1), 30-41. https://doi.org/10.1053/j.ajkd.2017.12.012
25. Schäfer-Keller, P., Steiger, J., Bock, A., Denhaerynck, K., & De Geest, S. (2008). Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant*, *8*(3), 616-626. https://doi.org/10.1111/j.1600-6143.2007.02127.x
26. Zelikovsky, N., & Schast, A. P. (2008). Eliciting accurate reports of adherence in a clinical interview: development of the Medical Adherence Measure. *Pediatr Nurs*, *34*(2), 141-146.
27. Mikulski, B. S., Bellei, E. A., Biduski, D., & De Marchi, A. C. B. (2022). Mobile Health Applications and Medication Adherence of Patients With Hypertension: A Systematic Review and Meta-Analysis. *Am J Prev Med*, *62*(4), 626-634. https://doi.org/10.1016/j.amepre.2021.11.003
28. Gurcay, B., Yilmaz, F. T., & Bilgin, A. (2024). The Effectiveness of Telehealth Interventions on Medication Adherence Among Patients with Type 2 Diabetes: A Meta-Analysis. *Telemed J E Health*, *30*(1), 3-20. https://doi.org/10.1089/tmj.2023.0088
29. Rebafka, A. (2016). Medication Adherence After Renal Transplantation-a Review of the Literature. *J Ren Care*, *42*(4), 239-256. https://doi.org/10.1111/jorc.12181
30. Denhaerynck, K., Steiger, J., Bock, A., Schäfer-Keller, P., Köfer, S., Thannberger, N., & De Geest, S. (2007). Prevalence and risk factors of non-adherence with immunosuppressive medication in kidney transplant patients. *Am J Transplant*, *7*(1), 108-116. https://doi.org/10.1111/j.1600-6143.2006.01611.x
31. Woźniak, I., Kolonko, A., Chudek, J., Nowak, Ł., Farnik, M., & Więcek, A. (2018). Influence of Polypharmacy on the Quality of Life in Stable Kidney Transplant Recipients. *Transplant Proc*, *50*(6), 1896-1899. https://doi.org/10.1016/j.transproceed.2018.02.128
32. Eysenbach, G. (2005). The law of attrition. *J Med Internet Res*, *7*(1), e11. https://doi.org/10.2196/jmir.7.1.e11
33. Griva, K., Neo, H. L. M., & Vathsala, A. (2018). Unintentional and intentional non-adherence to immunosuppressive medications in renal transplant recipients. *Int J Clin Pharm*, *40*(5), 1234-1241. https://doi.org/10.1007/s11096-018-0652-6
34. Muduma, G., Shupo, F. C., Dam, S., Hawken, N. A., Aballéa, S., Odeyemi, I., & Toumi, M. (2016). Patient survey to identify reasons for non-adherence and elicitation of quality of life concepts associated with immunosuppressant therapy in kidney transplant recipients. *Patient Prefer Adherence*, *10*, 27-36. https://doi.org/10.2147/ppa.S96086
35. Schmid-Mohler, G., Thut, M. P., Wüthrich, R. P., Denhaerynck, K., & De Geest, S. (2010). Non-adherence to immunosuppressive medication in renal transplant recipients within the scope of the Integrative Model of Behavioral Prediction: a cross-sectional study. *Clin Transplant*, *24*(2), 213-222. https://doi.org/10.1111/j.1399-0012.2009.01056.x
36. Neuberger, J. M., Bechstein, W. O., Kuypers, D. R., Burra, P., Citterio, F., De Geest, S., Duvoux, C., Jardine, A. G.,

Kamar, N., Krämer, B. K., Metselaar, H. J., Nevens, F., Pirenne, J., Rodríguez-Perálvarez, M. L., Samuel, D., Schneeberger, S., Serón, D., Trunečka, P., Tisone, G., & van Gelder, T. (2017). Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation*, *101*(4S Suppl 2), S1-s56. https://doi.org/10.1097/tp.0000000000001651

37. Low, J. K., Williams, A., Manias, E., & Crawford, K. (2015). Interventions to improve medication adherence in adult kidney transplant recipients: a systematic review. *Nephrol Dial Transplant*, *30*(5), 752-761. https://doi.org/10.1093/ndt/gfu204

38. Zhu, Y., Zhou, Y., Zhang, L., Zhang, J., & Lin, J. (2017). Efficacy of interventions for adherence to the immunosuppressive therapy in kidney transplant recipients: a meta-analysis and systematic review. *J Investig Med*, *65*(7), 1049-1056. https://doi.org/10.1136/jim-2016-000265

39. De Bleser, L., Matteson, M., Dobbels, F., Russell, C., & De Geest, S. (2009). Interventions to improve medication-adherence after transplantation: a systematic review. *Transpl Int*, *22*(8), 780-797. https://doi.org/10.1111/j.1432-2277.2009.00881.x

40. Chen, H., Liu, S., Yu, L., Hou, X., & Zhao, R. (2024). Factors and interventions affecting tacrolimus intrapatient variability: A systematic review and meta-analysis. *Transplant Rev (Orlando)*, *38*(4), 100878. https://doi.org/10.1016/j.trre.2024.100878

41. Xie, W., Fan, S., Liu, R., Yan, W., Su, C., Zheng, K., Wang, X., & Wang, Z. (2024). Tacrolimus intra-patient variability measures and its associations with allograft clinical outcomes in kidney transplantation. *Transplant Rev (Orlando)*, *38*(3), 100842. https://doi.org/10.1016/j.trre.2024.100842

42. Staatz, C. E., & Tett, S. E. (2015). Clinical Pharmacokinetics of Once-Daily Tacrolimus in Solid-Organ Transplant Patients. *Clin Pharmacokinet*, *54*(10), 993-1025. https://doi.org/10.1007/s40262-015-0282-2

43. Oh, C. K., Huh, K. H., Lee, J. S., Cho, H. R., & Kim, Y. S. (2014). Safety and efficacy of conversion from twice-daily tacrolimus to once-daily tacrolimus one month after transplantation: randomized controlled trial in adult renal transplantation. *Yonsei Med J*, *55*(5), 1341-1347. https://doi.org/10.3349/ymj.2014.55.5.1341

Supplementary Files

Supplementary information.
URL: http://asset.jmir.pub/assets/aa22ed4c6cefbaa7253361e28ad6e449.docx

Figures

Fig. S1 Cochrane Risk of Bias tool for randomized trials (RoB 2.0).

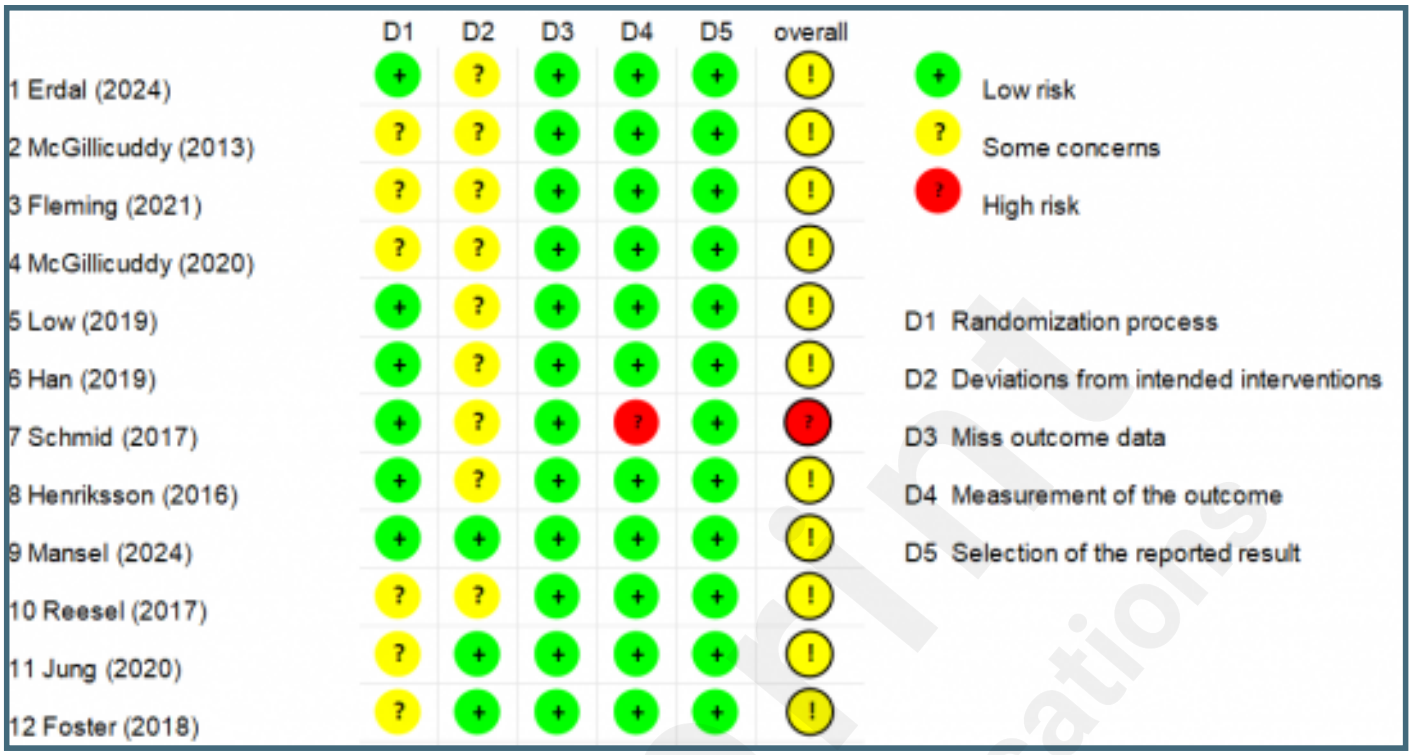
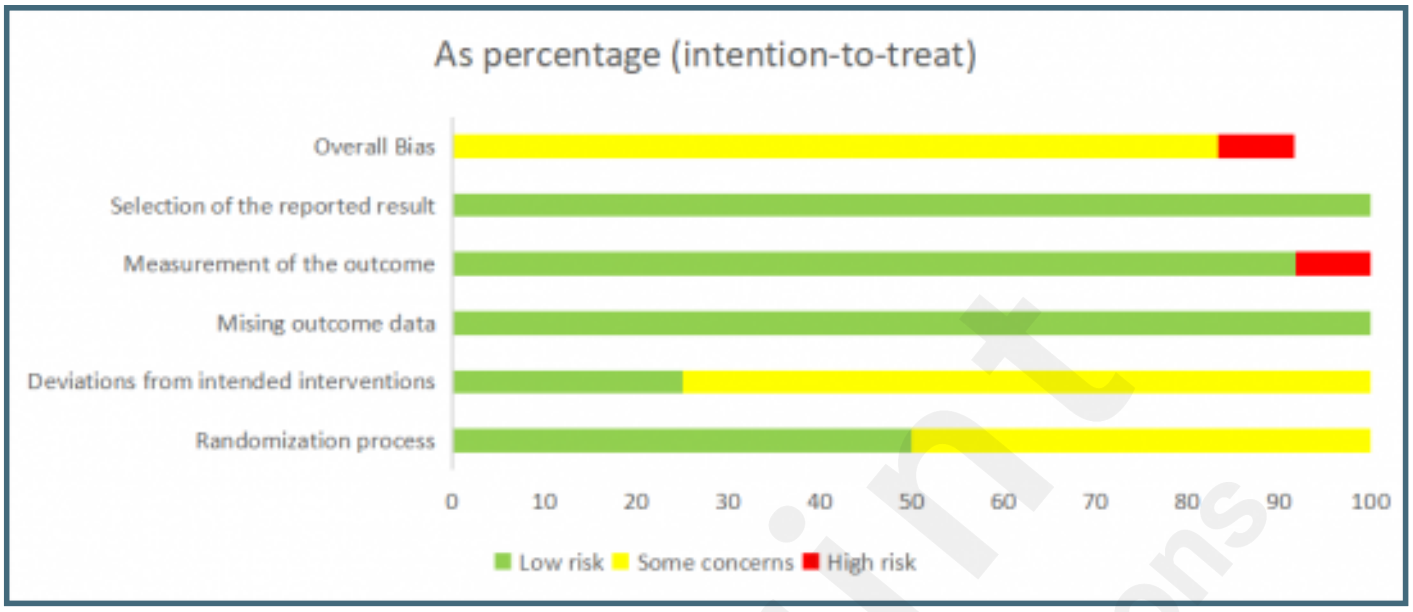


Fig. S2 Summary of bias risk of included studies.



CONSORT (or other) checklists

PRISMA checklist.
URL: http://asset.jmir.pub/assets/297e888171befb31449c85f2a3ad4efb.pdf