# Effects of eHealth Interventions on improving medication adherence in kidney Transplant Recipients: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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**Abstract**

Aims Immunosuppressant non-adherence is a prevalent problem leading to many adverse outcomes in Renal transplant recipients. eHealth has the potential to improve medication compliance, but evidence in kidney transplantation remains unclear. This review aims to explore the effects of eHealth interventions on improving medication compliance in Kidney transplantation. Methods A systematic search was conducted of the following databases: PubMed, Embase, Cochrane Library, CINAHL, and Web of Science Core Collection. The search included studies published up to July 22, 2021. Two authors selected relevant studies and extracted data independently. The quality of the literature was evaluated using the Cochrane collaborative bias risk tool. To estimate the effect size, a meta-analysis of the studies was performed using the Cochrane Collaboration software Review Manager 5.3 PRISMA guidelines were followed. Results Nine studies involving 777 patients were included. Compared with control group, eHealth interventions improved medication adherence measured by electronic monitoring (RR=1.46, 95%CI, 1.11 to 1.90, p=0.006) and decreased rejection (RR=0.38; 95%CI, 0.15 to 0.97, p=0.04). There was no difference in medication compliance measured by BAASIS (RR=1.03, 95% CI, 0.88 to 1.21, p=0.72), Tacrolimus level (MD=0.16, 95%CI, -0.21 to 0.52, p=0.39), coefficient of variation of tacrolimus level (MD=-0.01, 95%CI, -0.05 to 0.02, p=0.41), and kidney function (MD=-0.44, 95% CI, -8.32 to 7.43, p=0.91) between the two groups. Conclusions eHealth interventions can improve medication adherence in kidney transplantation in the short time. However more high-quality intervention studies need performing to determine whether eHealth improves long-term adherence and clinically relevant outcomes.

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A systematic search was conducted of the following databases: PubMed, Embase, Cochrane Library, CINAHL, and Web of Science Core Collection. The search included studies published up to July 22, 2021. Two authors selected relevant studies and extracted data independently. The quality of the literature was evaluated using the Cochrane collaborative bias risk tool. To estimate the effect size, a meta-analysis of the studies was performed using the Cochrane Collaboration software Review Manager 5.3 PRISMA guidelines were followed.

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Nine studies involving 777 patients were included. Compared with control group, eHealth interventions improved medication adherence measured by electronic monitoring (RR=1.46, 95%CI: 1.11 to 1.90, p=0.006) and decreased rejection (RR=0.38, 95%CI: 0.15 to 0.97, p=0.04). There was no difference in medication compliance measured by BAASIS (RR=1.03, 95%CI: 0.88 to 1.21, p=0.72), Tacrolimus level (MD=0.16, 95%CI: -0.21 to 0.52, p=0.39), coefficient of variation of tacrolimus level (MD=-0.01, 95%CI: -0.05 to 0.02, p=0.41), and kidney function (MD=-0.44, 95% CI: -8.32 to 7.43, p=0.91) between the two groups.

**Conclusions**

eHealth interventions can improve medication adherence in kidney transplantation in the short time. However more high-quality intervention studies need performing to determine whether eHealth improves long-term adherence and clinically relevant outcomes.

**Keywords:** eHealth; kidney transplant; medication adherence; telemedicine.

**Introduction**

The end-stage renal disease (ESRD) is a significant public health issue in the worldwide. The number of ESRD patients with need for the renal replacement therapy is estimated between 4.902 and 7.083 million(*1* ). Moreover, there is a growing trend(*2* ). In the United States, spending for ESRD patients totaled $35.9 billion, accounting for 7.2% of the overall Medicare paid claims in the fee-for-service system, and the share has remained relatively constant for a decade(*3* , *4* ).

Kidney transplantation (KTx) is the optimal therapy for ESRD. Compared to dialysis treatment, KTx is associated with a better psychosocial function, improved quality of life as well as lower costs and mortality (*5* ,*6* ). Although short-term outcomes after KTx are excellent, with a 96%-98%(*7* ) 1-year graft survival, long-term outcomes remain suboptimal, the 10-year graft survival remains low (67.8%) (*8* ). A key reason for the lack of improvement in long-term outcomes is poor adherence to immunotherapy regimen. As immunosuppressive therapy is often critical for KTx, they need to take immunosuppressants for life to prevent rejection. Unfortunately, findings from several studies have indicated that in solid organ transplant recipients, The highest rate of immunosuppressant non-adherence was found in KTx with a prevalence of 36-55% (*9* ). This low adherence may be due in part to complicated treatment regimens, not only due to the number of pills required, but also to frequent dose adjustments based on blood level monitoring, side effects and rejection episodes (*10* ). Additional barriers such as financial problems (*11* ), memory issues (*12* ), and communication barriers (*13* ).

New eHealth technologies offer potential solutions for improving medication adherence in KTx. The World Health Organization (WHO) broadly defines eHealth as the use of information and communication technologies (ICT) for health, including patient treatment, research, education of healthcare professionals, and public health monitoring (*14* ). Currently, with the rapid development of ICTs, eHealth interventions appear to be a useful tool for increasing medication adherence. The benefits of eHealth are widely acknowledged. It can contribute to achieving universal health coverage by overcoming geographical barriers, increasing access, and the provision of health services to remote populations and underserved communities (*15* ).

Previous meta-analyses describing the effect of eHealth intervention on the medication adherence of solid organ transplant patients have been published. Tang et al.'s (*16* ) meta-analysis suggests that eHealth

interventions may improve medication adherence in the short term. On the contrary, Lee et al.'s (*17* ) meta-analysis showed that the effects of the eHealth interventions were similar to those of the care provided to the control group. In addition, medication adherence varies widely among different types of transplant patients. Therefore, it is necessary to systematically evaluate whether eHealth interventions can improve medication compliance in KTx.

## Methods

All analyses were based on data from previously published studies. Thus, no ethical approval or patient consent was required. This systematic review was conducted following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines(*18* ).

### Information Sources

The following electronic databases were searched to identify relevant studies up to July 22, 2021: PubMed, Embase, Cochrane Library, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and Web of Science Core Collection. Additionally, we manually searched the references listed in the present review article to find further.

### Search and Eligibility Criteria

### Overall Search Strategy

The search was performed using a combination of the following keywords on July 22, 2020: ("kidney transplantation" or "kidney transplant*" or "renal transplant*") AND (e-health or eHealth or m-health or tele-Health or telemedicine or Internet or Software or website or telemanagement or telecommunications or tele-monitoring) AND ("patient compliance" or "medication adherence" or "noncompliance*"). The search strategies for each database are presented in Multimedia Appendix1. In addition, the search terms used for electronic databases were chosen following the PICO format (P: patients, kidney transplantation; I: intervention, eHealth; C: control [any control interventions], O: outcome [medication adherence]) and modified as necessary to include equivalent terms for each database.

### Studies

Randomized Controlled Trials (RCTs) regarding the effect of eHealth Interventions for patients with KTx were included in the review. The included studies were published in English. Articles were excluded if the study was a non-RCT or nonclinical trial. Abstracts from meeting proceedings with no corresponding full article published in a peer-reviewed journal or no specific data provided even after contacting the author were excluded.

### Participants

Trials consisting of patients receiving immunosuppressive therapy after kidney transplant. Combined grafts are not included (eg. kidney-pancreas).

### Interventions

For our study interventions, we included eHealth interventions. eHealth interventions include TeleHealth, Internet and computer-based, mobile health (such as applications and text messaging), Wearables, electronic medication dispenser and video Prior studies using various information and communication technology devices were considered. For our study controls, we included research control interventions that employed any reasonable interventions or usual care and did not involve the provision of eHealth interventions for improving medication adherence.

### Outcome Measures

The primary outcome measures were focused on medication adherence. We included medication adherence from studies involving eHealth interventions for transplant recipients as objective measures (medication compliance monitored by electronic devices, and clinical measures such as tacrolimus serum concentration levels,

coefficient of variation for blood tacrolimus level,the proportion of patients obtaining normal tacrolimus trough variability) and subjective measures (self-report questionnaires, such as Basel Assessment of Adherence to Immunosuppressive Medication Scale). Secondary outcome includes renal function, rejection and patient satisfaction.

**Search Methods for Identification of Studies**

Two authors (ZY and GXH) independently reviewed the search results and screened the titles, abstracts, and full texts of identified references to select potentially eligible studies, which were imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA).

**Data Extraction and Management**

Two independent reviewers (ZY and GXH) screened the titles and abstracts for potentially eligible studies identified by the primary search, and then reviewed the full texts to evaluate their final eligibility. The two authors cross-checked each other's articles, and, in the case of any disagreement regarding extracted data, a third author (LY) was brought into the discussion. Decisions were made based on consensus.

After selecting articles for inclusion, we extracted the following data along with the intervention characteristics: first author, publication year, publication country, sample size, average patient age, intervention duration, intervention group, control group, follow-up time, outcomes.

**Quality Assessment**

The methodological quality of the included studies was assessed by two independent reviewers (ZY and GXH), and inconsistencies were solved by consensus or involving a third researcher (LY). We followed the criteria of the Cochrane Collaboration risk-of-bias tool as guides. The quality items assessed were selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants, personnel, and outcome assessors), attrition bias, measurement bias, reporting bias, and other bias.

**Statistical Analysis**

This meta-analysis was performed using the Review Manager software (RevMan V.5.3; Cochrane Collaboration, Oxford, UK). Cochrane Q statistics and Chi-square test was used to determine whether heterogeneity existed among studies. If the heterogeneity ($p<0.1$, $\mathbf{I^2}$ >50%), the random effects model was used for meta-analysis. If there was no significant heterogeneity between studies (P[?]0.1, P[?]50%), The fixed effects model is adopted. For dichotomous variables, relative risk (RR) and 95% confidence interval (CI) were used. For continuous variables, when the measuring tools and units used in each document for an index are completely the same. The weighted mean difference (WMD) and 95% CI were used to represent. When they are not completely the same, standard mean difference (SMD) and 95% CI are used. A $P<0.05$ was considered to be statistically significant. For outcome where quantitative data cannot be synthesized, narrative analysis is performed. Since the number of studies that included the results of the meta-analysis was not more than 10, we did not use funnel plot for publication bias.

**Results**

**Search and Selection**

Of 1039 records identified, 224 were duplicates and 770 were excluded after abstract review for the reasons shown in Figure 1. The remaining 45 citations were retrieved for full-text review, and 9 trials met the inclusion criteria. Of the 9 included trials, 4 trials had available data for meta-analysis, whereas the other trials were assessed descriptively.

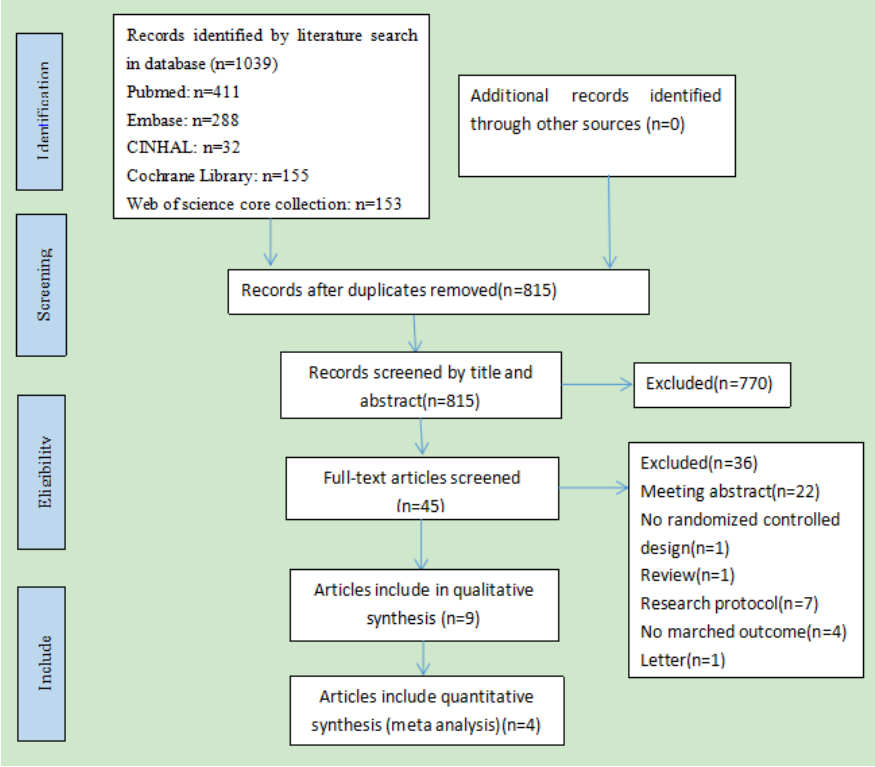


**Figure 1.** Selection of studies

### Study Characteristics

The baseline descriptive characteristics (country, sample size and age) of the 9 studies included in the systematic review were summarized in Table 1. Four studies (*19 -22* )were from the United States, Korea had two studies(*23* , *24* ), the others originated from German(*25* ), Australia(*26* ), Sweden(*27* ). The mean age of KTx ranged from 42.4 to 53.6 years, and all studies included both men and women. The duration of the interventions ranged from 3 to 12 months. The longest follow-up was one year.

**Table 1.** Descriptive summary of included studies.

| First authors, Years, Country | Age (years) M ± SD median (IQR/range) (I/C) | Sample size (I/C) | Intervention (duration) | Control | Fellow-up time (months) | Outcome (measures) |
|---|---|---|---|---|---|---|
| Han, 2019, Korea | 45(35-54)/43(30-52) | 70/66 | Mobile application for medication manage-ment (6 months) | Education on the importance of adherence | 6 | Medication adherence—BAASIS Medication adherence—electronic monitoring medication 3.Kidney function—eGFR |

| | | | | | | |
|---|---|---|---|---|---|---|
| McGillicuddy, 2013, USA | 42.44/57.6 | 9/10 | Mobile phone-based medication monitoring (3 months) | Education related to post- trans-plantation medical care | 3 | Medication adherence—Russell et al.'s adherence score Patient satisfaction |
| Reese, 2017, USA | I1: 50 ± 12 I2: 50 ± 11 C: 49 ± 11 | 40/39/38 | Automated medication reminders with wireless pill bottle and physician notification (6 months) | Wireless pill bottle that provided no alerts | 6 | Medication adherence—BAASIS Medication adherence—wireless pill bottle openings 3.Tac level 4.CVs for Tac level 5.The proportion of patients obtaining normal tacrolimus trough variability |
| Henriksson, 2016, Sweden | 44.3(9-68)/ 45.0(2-69) | 40:40 | Electronic medication dispenser (12 months) | Standard care | 12 | Medication adherence—electronic medication dispenser Tac level Rejection Kidney function—creatinine Cost-Effectiveness |

| | | | | | | |
|---|---|---|---|---|---|---|
| McGillicuddy, 2020, USA | 52.1 ± 11.3/ 51.5 ± 12.5 | 40/40 | An electronic medication tray with reminder capabilities enabled, a Bluetooth-enabled BP monitor, and the SMASK (Smartphone Medication Adherence Saves Kidneys) smartphone app. (6 months) | An electronic medication tray that provided no alerts and received text messages with healthy lifestyle tips | 12 | Medication adherence—the electronic Vaica medication trays The proportion of patients obtaining normal tacrolimus trough variability |
| Jung, 2020, Korea | 49.9±10.0/ 49.0±12.2 | 51/54 | Information and communication technology (ICT)-based centralized monitoring system. (6 months) | The ambulatory follow-up group | 6 | 1.Tac level 2.CVs for Tac level 3.Patient satisfaction 4.Kidney function—eGFR |
| Schmid, 2017, German | 46(18-59)/ 51(19-66) | 23/23 | Telemedically supported case management (12 months) | Standard aftercare | 12 | 1.Composite adherence percentage: Collateral reports (physicians, nurses) and the target tacrolimus trough levels 2.Acute rejection 3.Cost-Effectiveness |

| | | | | | | |
|---|---|---|---|---|---|---|
| Low, 2019, Australia | 53.6 (11.3)/ 48.4 (11.1) | 29/31 | A face-to-face meeting (a medication review and a consumer-centred video) and health coaching every two weeks, and medication event monitoring system (3 months) | Standard aftercare and medication event monitoring system | 12 | Medication adherence—BAASIS 2.Medication adherence—medication event monitoring system |
| Fleming, 2021, USA | 50.2(12.3)/ 51.2 (13.7) | 68/68 | mHealth app, clinical pharmacist–led supplemental medication therapy monitoring and management. (12 months) | Standard aftercare | 12 | The proportion of patients obtaining normal tacrolimus trough variability Patient satisfaction |

BAASIS, Basel assessment of adherence with immunosuppressive medication scales; M, mean; SD, standard deviation; IQR, interquartile range; eGFR, estimate the glomerular filtration rate; CVs, Coefficient of variations; Tac, tacrolimus.

**Intervention Programs**

Most studies used only one eHealth intervention, and a small number of studies used a combination of two eHealth interventions. Details of the intervention for each study are as follows. In Han et al.(*24* ) study, the intervention group was provided with a mobile application for medication management. The features of the application included reminders that reported on the state of the medication, monitored the state of the participant's medication, and provided education on immunosuppressants. In McGillicuddy et al. (*19* , *20* ), the intervention group received customizable reminder signals (light, chime), phone calls or text messages at the prescribed dosing day and time. They were also contacted by text, email, or phone when alerts indicated medication non-adherence. In Reese et al.'s study (*21* ), the intervention group received reminders, in which a light on the bottle would illuminate and the cap would chime when the medication should be taken. If adherence decreased to $< 90\%$ every 2 weeks, the study coordinator would contact the participant by telephone. In Jung et al(*23* ), both patients and the medical staff received feedback in the form of texts and pill box alarms in the event of a dosage/dosing time error or a missed dose. In Fleming et al (*22* ), mHealth app provided patients with an accurate list of their medication regimen that was automatically updated from the electronic medical record (EMR), timely medication reminders, automated messages triggered by missed doses or scheduled health monitoring. In low et al(*26* ), the intervention consisted of a face-to-face meeting (a medication review and a consumer-centred video) and a series of 6 fortnightly telephone calls (health coaching). In Henriksson et al. (*27* ), at the prescribed time for taking the medication, the electronic medication dispenser (EMD) gave visual and audible signals. If the patient did not take their medication, the audible signal was repeated with increasing frequency for 120 minutes. Schmid et al. (*25* ) adopted telemedically supported case management, included (i) a chronic case management process for the first year

posttransplant; (ii) a case management process applicable for acute care situations; and (iii) a telemedically equipped team. Members comprised a transplant nurse case manager (TNCM) and two senior transplant physicians (STP: surgeon and nephrologist).

**Risk of Bias**

Figure 2 presents the results of the risk-of-bias assessment for each study separately, and Figure 3 summarizes the percentages of studies with low, unclear, and high risks of bias. The risk of bias of included trials was high or unclear for most domains (Figure 2). Random sequence generation was adequately described in 5 trials (56%) and unclear in 4 trials (44%). Allocation concealment was assessed as low risk of bias in 3 trials (33%), high risk of bias in 1 trial (11%) and unclear in the remaining 5 trials (56%). Of the 9 trials, three trials (33%) blinded the participants to the trial intervention, high risk of bias in only 1 trail (11%) and unclear in 5 trial (56%). Blinding of outcome assessors occurred in 4 trials (44%), high risk in 1 trial (11%) and unclear in 4 (44%). Six trials (67%) were considered as low risk of attrition bias and 11 trials (33%) were assessed as high risk. All trials (100%) were assessed to have low reporting bias. Eight trials (89%) were assessed as having low risk of other potential bias and unclear in 1 (11%). Overall methodological quality of evidence was considered fair. We were unable to assess publication bias due to the limited number of trials.

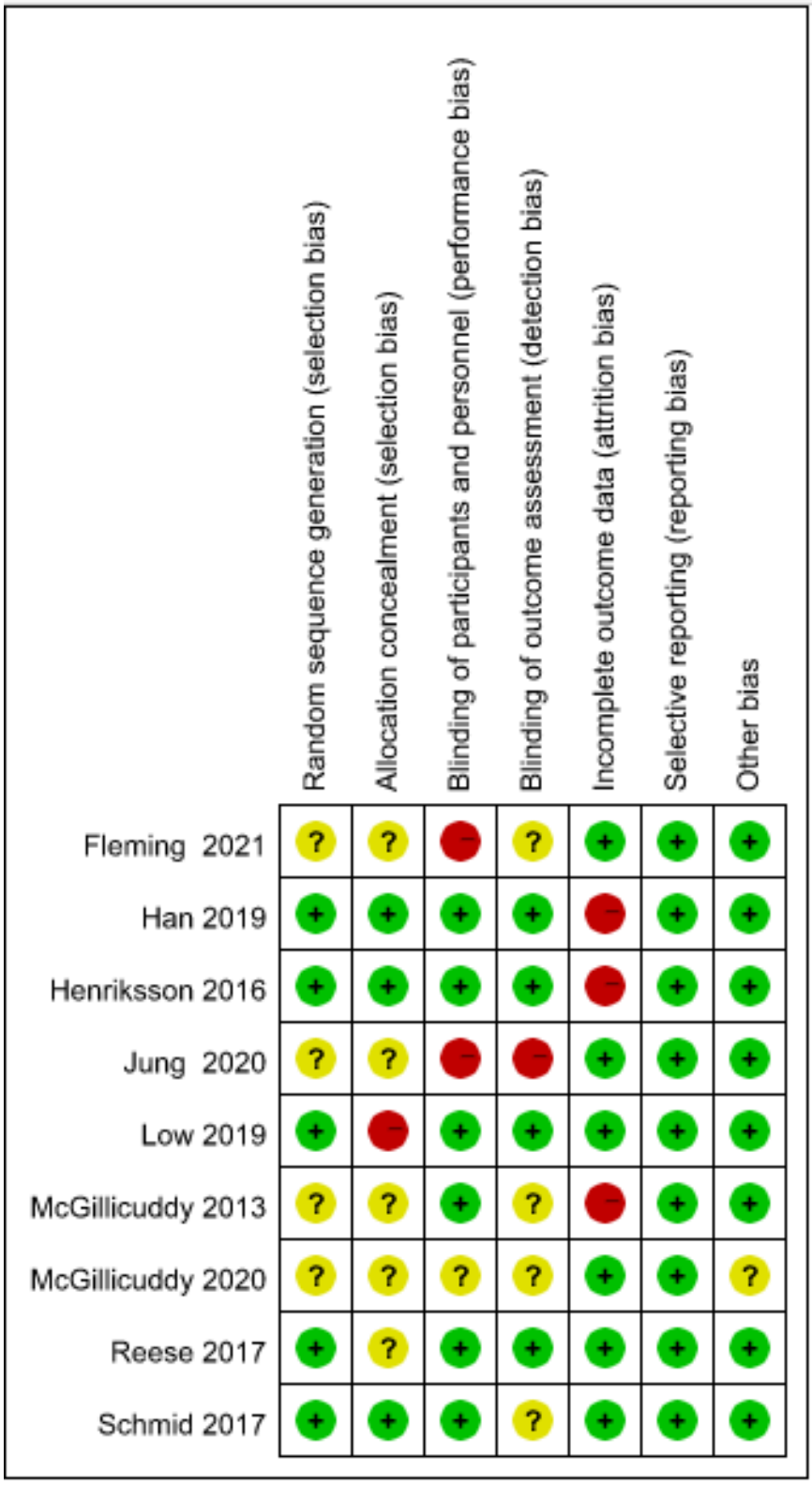

**Figure 2.** Risk of bias graph.

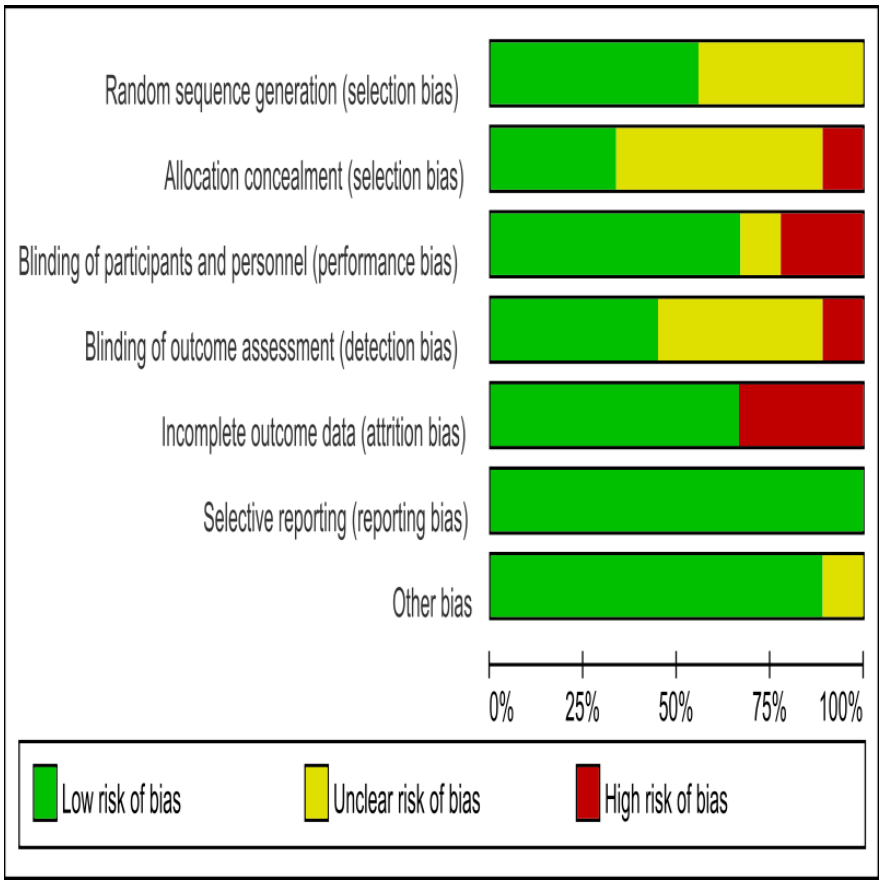


**Figure 3.** Risk of bias summary.

**Outcomes of Interest**

**Immunosuppressive Therapy Adherence as Assessed by Adherence Rate**

**Adherence rate assessed by electronic equipment**A total of 6 RCTs (*20* , *21* , *24* -*27* ) reported immunosuppressant adherence rate, and we were able to extract 3 sets of analyzable data from 5 RCTs with 344 participants in the meta-analysis. The random-effects model was used in this analysis owing to the moderate heterogeneity ($I^2$=53%, p=0.09). Results from the meta-analysis showed that participants in the eHealth intervention groups showed significantly increased adherence rate as compared with those in the routine intervention groups with a pooled RR = 1.46 (95%CI: 1.11 to 1.90, p=0.006)(Figure 4). We did not include Henriksson et al. (*27* ) because it only reported compliance rates (97.8%) in the intervention group, without an electronic medication dispener to record medication in control group. Low et al. (*26* ) did not give specific adherence rates, but instead presented the results in the form of a picture, they found no difference between the eHealth intervention and control groups. The study of Schmid et al. (*25* ) was not included in this analysis as a comprehensive adherence rate (combination of tacrolimus trough levels, collateral reports, and self-reported adherence rates) was used for analysis in that study.

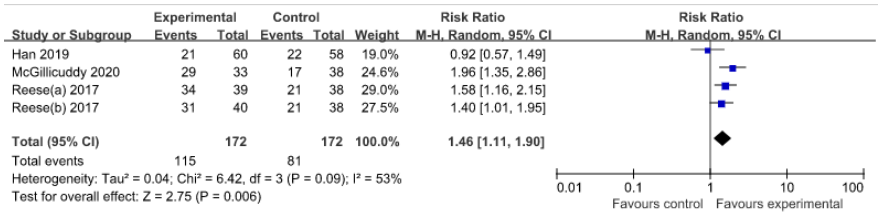


**Figure 4.** Forest plot of adherence rate by electronic equipment. Risk Ratio (RR) with 95% confidence interval (CI) between eHealth intervention group and control groups.

**Adherence rate assessed by questionnaires**Four RCTs(*19* , *21* , *24* , *26* ) used the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) to assess medication compliance. Sets of analyzable data from 2 RCTs (*21* , *24* ) with 261 participants in the meta-analysis. We used the fixed-effects model because of low heterogeneity among these studies ($I^2$=32%, p=0.23). Results of this meta-analysis found no significant group difference on medication adherence with the pooled MD=1.03 (95%CI: 0.88 to 1.21, p=0.72)(Figure 5). Low et al. (*26* ) did not give specific adherence rates, but instead presented the results in the form of a picture, they suggested the percentage of adherent participants decreased significantly between baseline and 3 to 12 months in the control group (p< 0.001) whilst the percentage of adherent participants in the eHealth intervention group remained constant over time. McGillicuddy et al. (*19* ) was not included in the analysis because the study used a self-designed medication compliance scores (the correct number of doses is combined with the prescribed time).

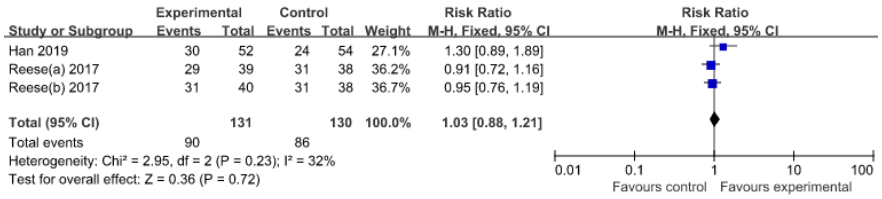


**Figure 5.** Forest plot of Adherence rate assessed by BAASIS. Risk Ratio (RR) with 95% confidence interval (CI) between eHealth intervention group and control groups.

### Blood Immunosuppressant Concentration

**Tacrolimus level**Two RCTs reported tacrolimus blood levels and the mean and standard differences were extracted from three(*21* , *23* , *25* ,*27* ). A total of 254 patients participated in these two studies and the fixed-effects model was used in this analysis owing to the no heterogeneity ($I^2$=0%, p=0.38). Results of this meta-analysis found no significant group differences on the Tacrolimus level MD = 0.16 (95% CI: -0.21 to 0.52, p = 0.39)(Figure 6). While other (*27* ) did not provide analyzable data or median and mean, thus precluding the possibility for combining these statistics with other data. Henriksson et al. (*27* ) found there was no significant difference in tacrolimus concentration between the 2 groups over the 1-year follow-up period.

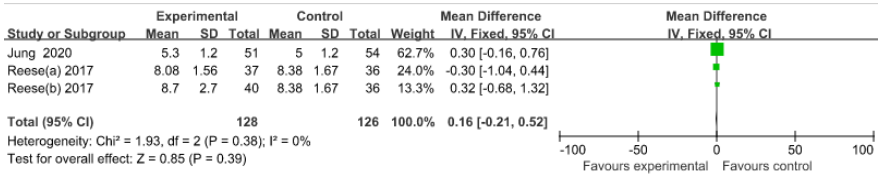


**Figure 6.** Forest plot of Tacrolimus level. Risk Ratio (RR) with 95% confidence interval (CI) between

eHealth intervention group and control groups.

**Coefficient of variation for blood tacrolimus levels**Two RCTs have reported this variable. A total of 244 patients participated in these two studies and the fixed-effects model was used in this analysis owing to the no heterogeneity ($I^2$=0%, P=0.89). Results of this meta-analysis found no significant group differences on the Coefficient of variation for blood tacrolimus levels MD = -0.01(95% CI: -0.05 to 0.02, p=0.41)(Figure 7).

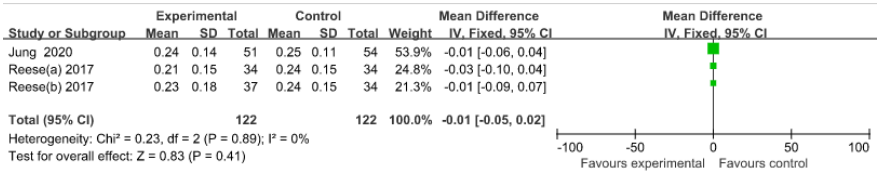


**Figure 7.** Forest plot of coefficient of variation for blood tacrolimus levels. Mean Difference (MD) with 95% confidence interval (CI) between eHealth intervention group and control groups.

**The proportion of patients obtaining normal tacrolimus trough variability**

Fleming et al.'s 12-month randomized controlled trial of 136 kidney transplant patients showed that more patients in the pharmacist-led mHealth-based intervention group achieved a tacrolimus coefficient of variation of less than 30% compared to the control group(P=0.0133). McGillicuddy et al. (*20* ) also found improvement in the proportion of patients achieving a clinical goal of a tacrolimus intrapatient variability of <40% (80% vs 70%, P = 0.001) in the intervention group as compared to the control group.

**4. Kidney function**

Two RCTs assessed kidney function using eGFR. These studies included 241 participants and the random-effects model was used in this analysis owing to the high heterogeneity ($I^2$=66%, p=0.08). Results of this meta-analysis found no significant group differences on eGFR, with the pooled MD = -0.44(95% CI: -8.32 to 7.43, p=0.91)(Figure 8).

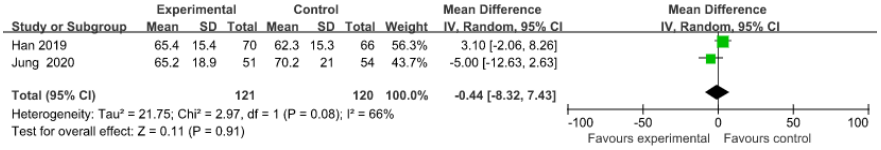


**Figure 8.** Forest plot of eGFR. Mean Difference (MD) with 95% confidence interval (CI) between eHealth intervention group and control groups.

Henriksson et al. (*27* ) found that average P-creatinine level was slightly lower in the eHealth intervention group than the control group (131vs.150μmol/L, not significant).

**5.Rejection**

Two RCTs assessed rejection. A total of 120 patients participated in these two studies and the fixed-effects model was used in this analysis owing to the no heterogeneity ($I^2$=0%, P=0.80). Results from the meta-analysis showed that participants in the eHealth intervention groups showed significantly decreased rejection as compared with those in the routine intervention groups with a pooled RR =0.38 (95%CI: 0.15 to 0.97, p = 0.04)(Figure 9).


**Figure 9.** Forest plot of rejection. Risk Rate (RR) with 95% confidence interval (CI) between eHealth intervention group and control groups.

### 6.Patientsatisfaction

Patient satisfaction was measured in only three of nine reviewed studies. McGillicuddy et al. (*19* ) assessed the effect of text reminders and electronic medication tray with reminder function on Medication Compliance. Participants reported high overall satisfaction with the mHealth system (average score 4.8/5 point Likert scale: 1= strongly disagree-5 = strongly agree). In Fleming et al(*22* ) study, the mHealth app has personalized reminders, including timely medication reminders, automated messages triggered by missed doses or scheduled health monitoring. 93% of participants were satisfied with the simple use of mHealth app. Jung et al. (*23* ) assessed the effect of with texts and pill box alarms on medication adherence and their research suggested that overall satisfaction with the information and communication technology (ICT)-based centralized monitoring system was higher than neutral, even though most users were in their 50s or older.

**Cost-Effectiveness**Economic evaluations were carried out in only two of nine reviewed studies. Two studies have shown that eHealth intervention can improve medication compliance(*25* ) and reduce rejection(*27* ), with significant cost saving by, for example, fewer admission rates and shorter lengths of unplanned hospitalization(*25* ), and reductions the cost of diagnosis and treatment of rejection(*27* ). It is important to note that neither study fully assessed direct and indirect costs, which limits the reliability of the conclusions.

## Discussion

To our knowledge, this systematic review and meta-analysis is the first to systematically assess the influence of eHealth interventions in improving medication adherence to patient with KTx. 9 eligible studies were identified, and our meta-analysis included data from 4 studies. This systematic review included only RCTs with a high level of evidence among interventional studies. Our findings suggest that eHealth can improve medication compliance and decreased rejection in kidney transplant patients in the short term as well as guidance regarding the development of eHealth interventions. Data were sparse for most other outcomes. We believe that more trials are needed to determine the clinical outcomes of eHealth interventions on transplant kidney function, rejection, and Patient-centered patient outcomes report (eg, patient satisfaction).

Previous studies, though, have provided a systematic review of compliance interventions in the kidney transplant population,But a result with only a descriptive analysis and no quantitative synthesis can affect the effectiveness of the results (*28* ). Additionally, another meta-analysis included studies that showed compliance interventions improved medication compliance in KTx (*29* ), but more reported non-eHealth interventions, such as behavioral and cognitive interventions or medication knowledge improvement. Recently, some meta-analyses on medication compliance in solid organ transplantation have been published. Shi et al. (*10* ) performed subgroup analysis according to organ type and found that compliance intervention could improve medication compliance with KTx. The meta-analysis of Lee et al. (*17* ) on solid organ transplantation including kidney transplantation showed that the results of eHealth intervention were similar to that of routine care intervention. The effect of eHealth intervention on medication compliance in kidney transplant patients is not clear. This highlights the importance of this study.

Our review used different models of eHealth intervention. For example, some studies only used mobile apps, while others used electronic medication dispenser, a consumer-centred video, or comprehensive intervention (e.g., electronic medication dispenser and physician notification). In addition, optimal type, frequency and duration of electronic intervention are unclear. Further research is needed in the later stage.

KTx remains the gold standard for the treatment of most ERSD. Due to limited resources for health care expenditure, Long-term survival of transplanted kidneys is important for patient health and public health resources. The long-term effects and economic benefits of eHealth interventions for KTx are unclear. In our study, the longest follow-up time after intervention was 12 months and the shortest was only 3 months. Due to the short duration of follow-up, this highlights the need for long-term follow-up in the future.

This review found few articles examined patient satisfaction and preferences for particular types of eHealth interventions. Three studies (*19* , *22* , *23* ) assessed patient satisfaction, and most patients were satisfied with the electronic devices used in eHealth interventions. Satisfaction may indirectly affect patient utilization. Other studies did not report patient satisfaction. But the use of electronic devices was reported. Han et al. (*24* ) shown over one-half of the patients stopped using the Adhere4U application within the first month, and only 10% of the remaining patients were using the app up to the end of the study. Low et al. research (*26* ) showed 42% of patients underutilized Medication Event Monitoring System during the 12-month intervention. A high attrition rate might have lowered the overall size of the effect of intervention(low). The results on satisfaction are inconclusive. There is need for more studies to evaluate user satisfaction with eHealth interventions targeted at improving medication adherence to kidney transplant patient.

### Subgroup Analysis and Sensitivity analysis

Due to the limited data included in the meta-analysis, no subgroup analysis was performed. Through the sensitivity analyses, we found that excluding studies one by one did not significantly alter the effect of eHealth intervention on medication adherence.

### Publication bias

We did not perform the funnel plot to illustrate the publication bias of the primary outcome because less than 10 articles were included.

### Limitations

The limitations of this study are as follows. First, we included only English literature. Ignore articles published in other languages. Second, we did not search for grey literature and unpublished studies. Additionally, articles did not provide specific values, but presented the research results in the form of charts or words, which affected the results of meta-analysis. It is worth mentioning that despite the rapid development of information technology, the research in this paper is all from developed countries. Finally, these variations might contribute to bias. Due to the limited number of articles, we did not use funnel plots for publication bias, so we are not sure about publication bias. However, given that some studies have reported negative results, we have reason to believe that the possibility of release bias is low.

### Conclusions

Results of our meta-analysis showed that eHealth intervention improved medication compliance and reduced rejection in KTx compared with the control group in the short time. Therefore, eHealth interventions can be used for medication adherence in KTx. For future studies, RCTs with a larger sample size and a long-term follow-up are necessary to overcome the shortcomings of current trials.

### Data statement

The data in our systematic review and meta-analysis have been provided in the manuscript.

### Conflicts of interest

All authors have no conflict of interest.

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Not applicable.

### Authors' contributions

Yue Liu and Xiaohong Guan contributed to the determination of study topic and design of the study. Yue Liu and Yun Zhang mainly conducted the article search, extracted the data, performed the assessment of methodological quality of enrolled studies and pooled the results. Yue Liu contributed to the original manuscript writing. Xiaohong Guan was in charge of oversight and leadership responsibility for the research activity planning and execution. All authors approved the final version of the manuscript to be published.

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