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Efficacy of interventions for adherence to the immunosuppressive therapy in kidney transplant recipients: a meta-analysis and systematic review

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ABSTRACT

Immunosuppressive treatment regimens are complex and require ongoing self-management. Medication adherence can be difficult to achieve for several reasons. The current meta-analysis and systematic review investigated whether adherence interventions improved immunosuppressive treatment adherence in kidney transplant recipients. Medline, Cochrane, EMBASE, and Google Scholar were searched until October 17, 2016 using the following search terms: kidney transplantation, compliance, adherence, and immunosuppressive therapy. Randomized controlled trials and two-arm prospective, retrospective, and cohort studies were included. The primary outcomes were adherence rate and adherence score. Eight studies were included with a total for 546 patients. Among participants receiving intervention, the adherence rate was significantly higher than the control group (pooled OR=2.366, 95% CI 1.222 to 4.578, p=0.011). Participants in the intervention group had greater adherence scores than those in the control group (pooled standardized difference in means =1.706, 95% CI 0.346 to 3.065, p=0.014). Sensitivity analysis indicated that findings for adherence rate were robust. However, for adherence score, the significance of the association disappeared after removing one of the studies indicating the findings may have been overly influenced by this one study. Intervention programs designed to increase immunosuppressive adherence in patients with kidney transplant improve treatment adherence.

Significance of this study

What is already known about this subject?

- About 60% of late acute rejection and 30–35% of graft loss is due to non-adherence.
- In addition, the rate of non-adherence in patients with kidney transplant ranges from 15% to 55%.
- Risk factors for non-adherence include longer time post-transplantation, financial strain, depression, younger age, social isolation, and low cognition.

What are the new findings?

- Among participants receiving adherence intervention, the adherence rate was significantly higher than the control group.
- Participants in the intervention group had greater adherence score than those in the control group.
- In conclusion, this adherence intervention significantly improved adherence to immunosuppressive therapy in patients with kidney transplant.

How might these results change the focus of research or clinical practice?

- Improving adherence to immunosuppressive therapy in patients with kidney transplant is necessary for better prognosis.
- How to measure the adherence in patients with kidney transplant effectively is an important issue.
- Additional studies are necessary to better understand what types of intervention are most effective, and to gain greater insight into the impact of intervention on clinical outcomes.

INTRODUCTION

In the past decades, immunosuppressive drugs and improved surgical techniques have increased the 1-year graft survival in kidney transplantation; however, the 10-year kidney transplant function remains low (50%).[1] One reason for the lack of improvement in long-term outcomes is poor adherence to immunosuppressive therapy.[2] Up to 60% of late acute rejection and about 30–35% of graft loss is due to non-adherence.[3–5] The rate of non-adherence in patients with kidney transplant ranges from 15% to 55%.[6–9] Prior studies have found that non-adherence to medications leads to suboptimal outcomes and has been seen in almost half of graft losses.[2 10 11] Non-adherence is associated with decreased graft function, increased risk of kidney loss, and premature death.[12]

Immunosuppressive treatment regimens are complex and require ongoing self-management.

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Medication adherence can be difficult to achieve for several reasons including cost, dosing complexity, duration of treatment, forgetfulness, other priorities, and decision to omit a dose.[13] In addition, the presence of serious side effects of immunosuppressive treatment and the patient's appraisal of these side effects can impact adherence.[14 15] These side effects can include Cushingoid appearance, acne, weight gain, increased infection rate, diarrhea, and insomnia.[16] Risk factors for non-adherence include longer time post-transplantation, financial strain, depression, younger age, social isolation, and low cognition.[7 17–20]

Several studies have evaluated the methods used to improve adherence of treatment in patients with kidney transplants and improve transplantation outcomes. Interventions such as electronic monitoring feedback and cognitive education have shown benefit in improving adherence.[21] Other types of interventions are multicomponent and can involve incorporating personalized care planning, education, psychosocial support, decision aids, and self-monitoring tools.[22] This study investigated whether adherence interventions improve adherence of kidney transplant recipients to immunosuppressive regimens.

METHODS

Search strategy

Medline, Cochrane, EMBASE, and Google Scholar were searched up to October 17, 2016 using the following search terms: kidney transplantation, compliance, adherence, and immunosuppressive therapy. Randomized controlled trials (RCTs), two-arm prospective, retrospective, and cohort studies were included. Eligible studies had to have evaluated patients with solitary kidney transplants who were taking maintenance immunosuppressive regimen (s) following transplant surgery. Patients also must have received interventions to promote better adherence. Included studies also had to have reported quantitatively outcomes of interest. Letters, comments, editorials, case reports, proceedings, and personal communications were excluded. The list of potential studies was reviewed by two independent reviewers. In the case of uncertainty regarding eligibility, a third reviewer was consulted.

Data extraction and quality assessment

The following information/data were extracted from the included studies: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, and the major outcomes.

The quality of the included studies was assessed using the Cochrane Collaboration's tool for assessing risk to assess the included studies.[23]

Outcome measures

The primary outcomes were adherence rate and adherence score. Determination of adherence rate used methods, such as refill records, electronic medical caps that monitored each time the bottle opened, or patient surveys, to monitor drug use. Adherence score predicts a patient's adherence by identifying lapses in patient medication adherence. Adherence score takes into consideration whether the patient took a medication on a given day and if it was taken within a certain time frame.

Statistical analysis

OR was used as the measure of effect size for adherence rate, while standardized difference in means were used for adherence score. An OR>1 indicated benefit favoring intervention, and a standardized difference in means of adherence score indicated a beneficial effect for intervention. Study heterogeneity was presented using a χ^2-based Cochran's Q statistic and I^2. For the Q statistic, $p<0.10$ was considered statistically significant for heterogeneity. For the I^2 statistic, $I^2<25\%$ indicated low heterogeneity while $I^2>75\%$ indicated high heterogeneity. A DerSimonian-Laird random-effects model was performed to calculate pooled estimates of standardized difference in means across studies.[24] Leave-one-out sensitivity analyses were performed to evaluate whether any single study might have overly impacted the pooled results. A two-sided $p<0.05$ was considered significant. All statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, V.2.0 (Biostat, Englewood, New Jersey, USA).

RESULTS

The database searches identified 109 potential studies (figure 1), of which 60 were excluded due to being duplicates or not being relevant to our analysis. Forty-nine studies underwent full-text review, and 41 were eliminated for not reporting outcomes of interest, not having an adherence intervention, for being an abstract, being an ongoing study, and evaluating patients with liver or kidney transplant.

A total of eight studies were included encompassing 546 patients (ranging from 15 to 130 patients per study) (table 1).[25–32] Six of the included studies were randomized trials, and the other two studies were prospective. One study reported results for underage population, others recruited patients with the mean age ≥40 years, with a greater percentage of the population being male. The shortest duration of follow-up was 3 months. The intervention protocols used varied across studies (table 1).

Meta-analysis

Six studies provided information regarding adherence rate and were included in the meta-analysis. No significant heterogeneity among the five studies was observed ($Q=8.8$, $p=0.116$, $I^2=43.4\%$). The pooled analysis found that among participants receiving adherence intervention, the adherence rate was significantly higher than the control group (pooled OR=2.366, 95% CI 1.222 to 4.578, $p=0.011$) (figure 2A).

Three studies were included in the analysis for evaluation of the effect of intervention on adherence score. Large heterogeneity was observed in the data across studies ($Q=12.3$, $p=0.002$, $I^2=83.8\%$). The pooled analysis indicated that participants in the intervention group had greater adherence score than those in the control group (pooled standardized difference in means =1.706, 95% CI 0.346 to 3.065, $p=0.014$) (figure 2B).

Sensitivity analysis

Sensitivity analysis, in which each study was removed in turn, found that for adherence rate and adherence score, the removal of one study (Garcia *et al* for adherence rate

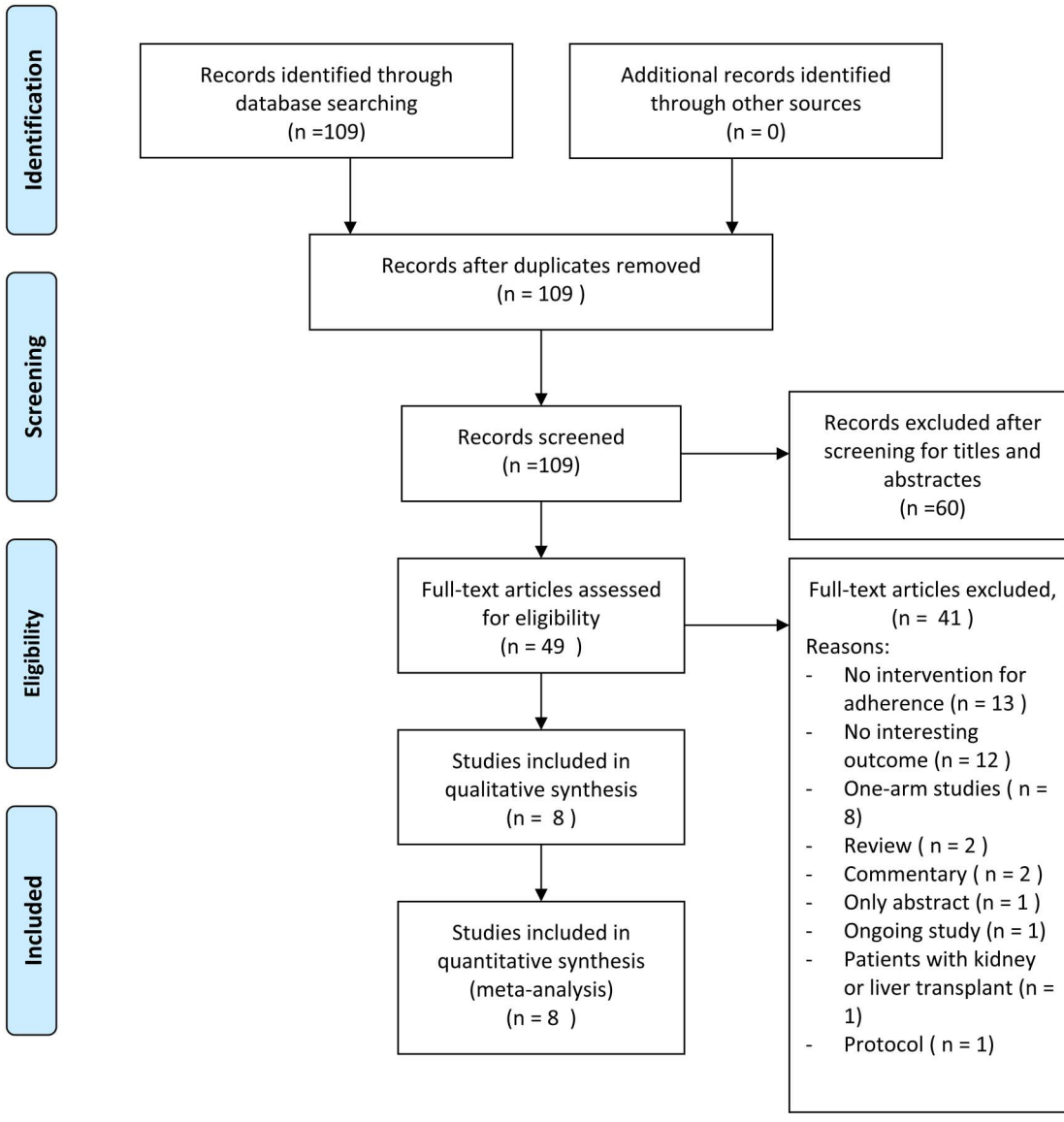


Figure 1 PRISMA flow diagram.

and Russell *et al* for adherence score) resulted in the loss of the significance of the association, indicating the findings may have been overly influenced by these individual studies (figure 3A, B).

Quality assessment

We used Cochrane Collaboration's tool for assessing risk of bias in the included studies (figure 4). Six studies had low risk of selection bias in random sequence generation, five studies had low risk of attrition bias, and all included studies had low risk of reporting bias. However, only three studies had low risk of bias in allocation concealment and blinding of outcome assessment. All studies had high risk of bias in blinding of participants and personnel. This was anticipated due to the characteristics of adherence intervention. Overall, the included studies had acceptable quality in random sequence generation, incomplete outcome data, and selective reporting.

DISCUSSION

Poor adherence to immunosuppressive therapy can negatively impact long-term outcomes in patients with kidney transplant. Outcomes of renal transplants are significantly affected by the ability of the transplant recipient to adhere to a complex and ongoing self-management regimen. This study found that adherence intervention through a pharmacist, intervention groups, or continuing education resulted in significantly increased adherence rate and adherence score compared with patients who did not receive adherence intervention. The findings support the idea that adherence intervention improves adherence to immunosuppressive therapy in patients following kidney transplantation.

The importance of improving non-adherence of patients with renal transplant to immunosuppressive therapy is indicated by the findings of several studies. Butler *et al*[6] performed a systematic review and meta-analysis that assessed the size of impact of non-adherence on graft failure in

Table 1 Summary of characteristics of included studies

First author (year)	Study design	Intervention groups	Intervention protocol	Number of patients	Mean age (year)	Male (%)	Immunosuppressive therapy	Length of follow-ups
Bessa (2016)[25]	RCT	Pharmaceutical care	Pharmacist's contribution to the care of individuals to optimize medicines use and improve health outcomes	62	45.8	59.40	Tacrolimus, prednisolone, mycophenolate sodium, or azathioprine	3 months
		Control	NR	62				
Garcia (2015)[32]	RCT	Continuing education	Continuing education	55	46	56.40	Tacrolimus—92.7% Cyclosporine—1.8% Mycophenolate—81.8% Azathioprine—16.4% Prednisone—100%	12 months
		Control	Standard care	56	49.29	62.50	Tacrolimus—94.6% Cyclosporine—0% Mycophenolate—80.4% Azathioprine—21.4% Prednisone—100%	12 months
Joost (2014)[31]	Prospective	Intensified care group	Educational behavior and technique intervention	35	51	77.00	Cyclosporine A: 6 (17%) Tacrolimus: 29 (83%) Mycophenolic acid—sodium: 7 (20%) Mycophenolic acid—mofetil: 28 (80%) Steroids withdrawal within the first 8 days: 8 (23%)	1 year
		Control	Standard care	39	54	62.00	Cyclosporine A: 7 (18%) Tacrolimus: 32 (82%) Mycophenolic acid—sodium: 8 (21%) Mycophenolic acid—mofetil: 31 (79%) Steroids withdrawal within the first 8 days: 7 (18%)	
Chisholm-Burns (2013)[28]	RCT	Intervention group	Behavior contract intervention	76	52.78	56.60	Cyclosporine—8 (10.5%) Tacrolimus—68 (89.5%)	15 months
		Control	Standard treatment	74	51.32	55.40	Cyclosporine—7 (9.5%) Tacrolimus—67 (90.5%)	
McGillicuddy (2013)[29]	RCT	mHealth intervention	mHealth system with reminder via smartphone	9	42.44	44.40	NR	3 months
		Control	Standard care	10	57.6	70.00		
Russell (2011)[27]	RCT	Continuous self-improvement	Continuous self-improvement intervention	8	55	50.00	NR	6 months
		Control	Attention control management	7	44	42.90		
Chisholm-Burns (2001)[28]	RCT	With clinical pharmacist interaction	Clinical pharmacist–patient interaction over the telephone	12	49.2	75.00	Cyclosporine—8 (10.5%) Tacrolimus—68 (89.5%)	1 year
		Control	NA	12			Cyclosporine—7 (9.5%) Tacrolimus—67 (90.5%)	
Fennell (1994)[30]	Prospective	Family-based interventional program	Family-based interventional program with booklet and calendar	14	12	57.10	Azathioprine and Prednisone Cyclosporine	NR
		Control	Standard care	15		60.00		

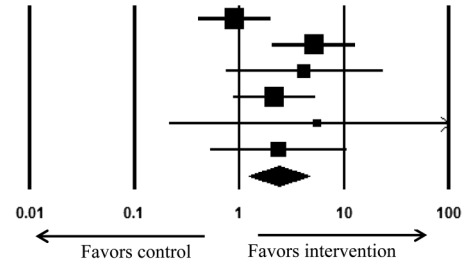
NR, not reported; RCT, randomized controlled trial.

patients with renal transplant. Their study included 36 studies. They found that non-adherence was common. For example, in cross-sectional studies, 22.3% of patients were non-adherent. Butler *et al* found that the odds of graft loss increased sevenfold in non-adherent subjects. Another study by Feldman *et al*[33] found patients missed about 4% of days of immunosuppressive therapy, 36% missed ≥4 consecutive doses, and that 16% missed ≥10 consecutive doses over a 2-month study period. Michelon *et al*[34] found an increasing rate of graft loss due to non-adherence over

A **Adherence rate**

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Weight (Random) Relative weight
Bessa (2016)	0.901	0.404	2.012	-0.254	0.800	25.79
Garcia (2015)	5.104	2.042	12.758	3.488	0.000	23.13
Joost (2014)	4.171	0.743	23.424	1.622	0.105	10.84
Chisholm-Burns (201	2.151	0.865	5.346	1.648	0.099	23.25
Chisholm (2001)	5.556	0.212	145.760	1.029	0.304	3.72
Fennell (1994)	2.364	0.529	10.555	1.127	0.260	13.27
Pooled	2.366	1.222	4.578	2.556	0.011	

Heterogeneity test: Q = 8.8, P = 0.116, I^2 = 43.4%



B **Adherence score**

Study name	Std diff in means	Lower limit	Upper limit	Z-Value	p-Value	Weight (Random) Relative weight
Garcia (2015)	0.782	0.396	1.168	3.971	0.000	39.50
McGillicuddy (2013)	3.295	1.913	4.676	4.675	0.000	28.71
Russell (2011)	1.417	0.283	2.551	2.449	0.014	31.78
Pooled	1.706	0.346	3.065	2.458	0.014	

Heterogeneity test: Q = 12.3, P = 0.002, I^2 = 83.8%

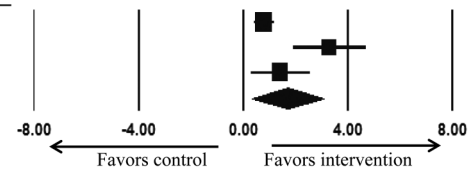
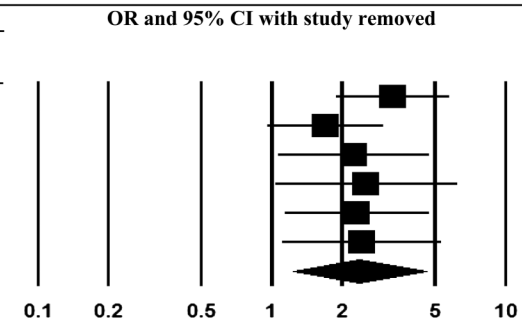


Figure 2 Forest plots for effect of intervention on (A) adherence rate and (B) adherence score.

A **Adherence rate**

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bessa (2016)	3.282	1.888	5.704	4.214	0.000
Garcia (2015)	1.686	0.957	2.970	1.808	0.071
Joost (2014)	2.226	1.061	4.672	2.116	0.034
Chisholm-Burns (2013	2.533	1.041	6.166	2.048	0.041
Chisholm (2001)	2.305	1.135	4.681	2.311	0.021
Fennell (1994)	2.420	1.100	5.324	2.196	0.028
Pooled	2.366	1.222	4.578	2.556	0.011



B **Adherence score**

Study name	Std diff in means	Lower limit	Upper limit	Z-Value	p-Value
Garcia (2015)	2.313	0.475	4.151	2.466	0.014
McGillicuddy (2013)	0.867	0.444	1.290	4.015	0.000
Russell (2011)	1.947	-0.509	4.403	1.554	0.120
Pooled	1.706	0.346	3.065	2.458	0.014

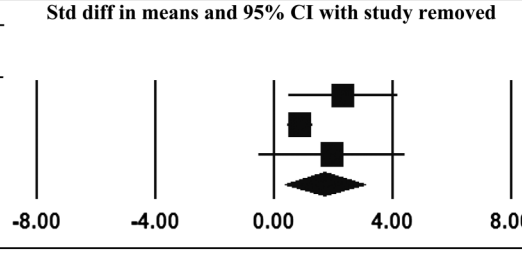


Figure 3 Sensitivity analysis for effect of intervention on (A) adherence rate and (B) adherence score.

three consecutive time periods, suggesting that the effect of non-adherence on graft loss rises over time.

Two studies evaluated the effect of different adherence intervention methods on adherence in patients following kidney transplants. Hardstaff *et al*[35] evaluated the use of smart top bottles compared with pill counting on adherence.[35] Smart top bottles have a cap with a microprocessor that records the date and time each time the bottle is opened. Patients also received regular structured interviews with a nurse practitioner. Hardstaff *et al* found smart tops

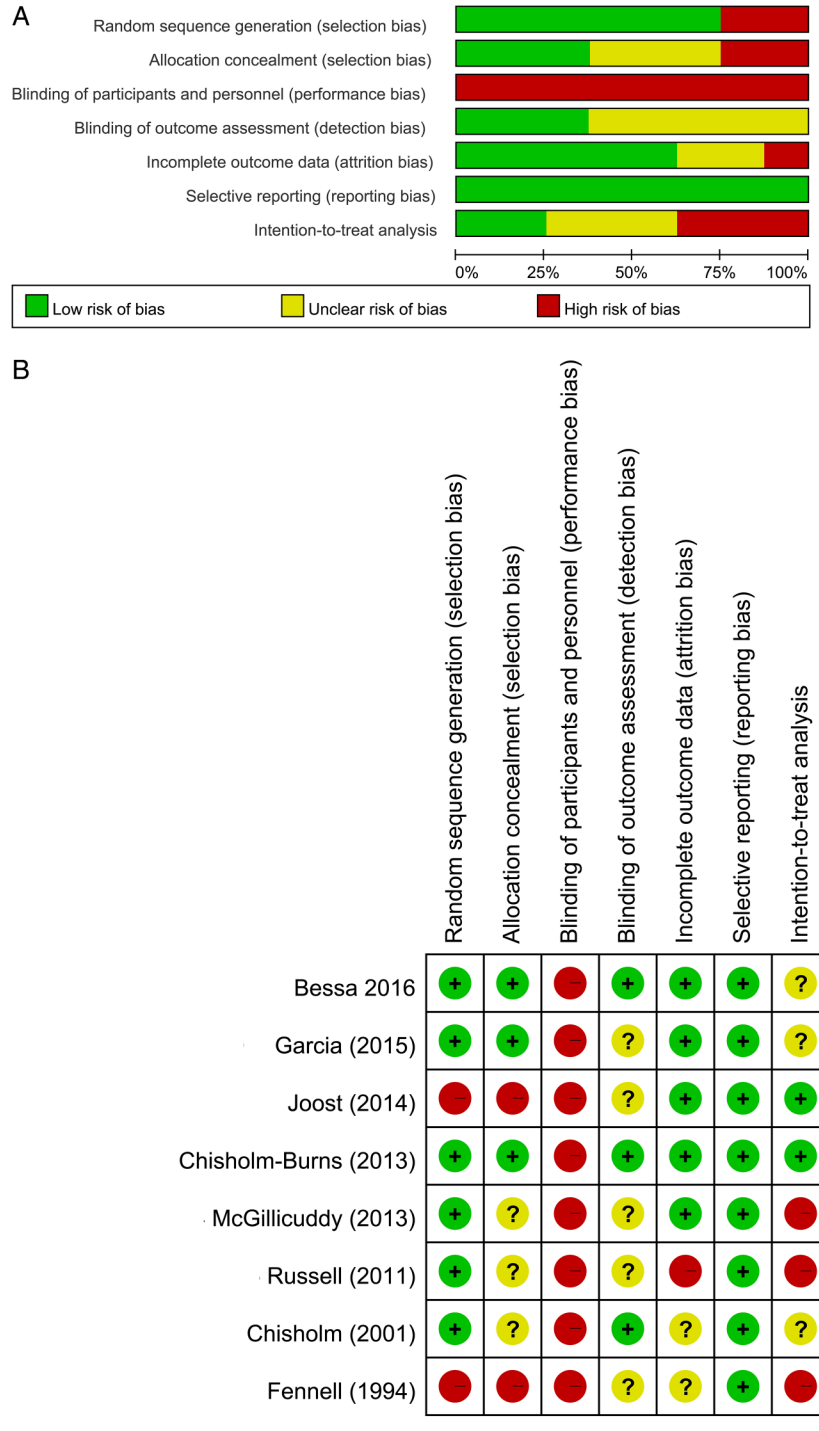


Figure 4 Quality assessment.

(electronic monitoring) and regular structured interviews were better at determining the number of doses taken, but non-adherence was still high and did not differ between groups (46% of patients in both groups missed at least one dose). In another study, Hardstaff *et al*[36] evaluated the efficacy of electronic monitoring feedback on adherence. All patients were given bottles with smart tops, but only one group was given feedback as measured via the smart top on their adherence at the first clinic visit (range 2–6 months following start of the study). Patients were followed for 12 months. They found no difference between the feedback and control groups with respect to adherence; at 12 months for both groups adherence worsened in about 40% of patients.

Several self-management strategies are used by patients with renal transplant to help improve adherence. Cedillo-Galindo and Gracida[37] found that the most common strategies to help improve adherence were use of a cell phone alarm (15.3%), use of alarm clocks (9.0%), schedules (5.6%), taking drugs at meals (5.1%), using a

drug record book (2.3%), and making the medication visible on the table (2.3%). A systematic review found kidney transplant recipients improve their self-management through achieving mastery and having an awareness of social accountability to the donor and the medical team.[22] Other factors that help to motivate patients to remain adherent include anxieties regarding rejection, complications, and comorbidities. Barriers to adherence include forgetfulness, fear of immunosuppressive therapy side effects, and inconsistent advice.[22] Self-management abilities appear to be impacted by patient age, donor type, and financial difficulties.[22]

There are several limitations to the study. The number of studies included was small. In addition, a large degree of heterogeneity in adherence score across studies was observed, which may reflect the diverse size of patient populations among the studies. The mode of adherence intervention also differed among the studies. Owing to the small number of included studies, it was not possible to perform subgroup analysis to evaluate the impact of different intervention programs. Measuring compliance is difficult and in some studies relied on patient recall which may have confounded the results.[35]

In conclusion, adherence intervention significantly improved adherence to immunosuppressive therapy in patients with kidney transplant. Additional studies are necessary to better understand what types of intervention are most effective, and to gain greater insight into the impact of intervention on clinical outcomes.

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