Renal transplantation for lupus nephritis: non-adherence and graft survival

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E Ntatsaki[1, 2], V S Vassiliou[3, 4], A Velo-Garcia[1, 5], A D Salama[6], D A Isenberg[1]

[1]Centre for Rheumatology, Division of Medicine, University College London, London, United Kingdom

[2]Rheumatology Department, Ipswich Hospital, Ipswich, United Kingdom

[3]Norwich Medical School, University of East Anglia, Norwich, United Kingdom

[4]Department of Medicine, Imperial College London, London, United Kingdom

[5]Internal Medicine Department, University Hospital Complex of Pontevedra, Pontevedra, Spain

[6]Centre for Nephrology, University College London, London, United Kingdom

Corresponding Author:

Eleana Ntatsaki, Centre for Rheumatology, Division of Medicine, University College London, London, United Kingdom. Email: ntatsakie@doctors.org.uk

Keywords Lupus nephritis, adherence to treatment, renal transplant, graft rejection, graft failure, systemic lupus erythematosus

Abstract

Objectives

Poor adherence to immunosuppressive treatment is common in patients with systemic lupus erythematosus and may identify those with lupus nephritis (LN) who have a poorer prognosis. Non-adherence has also been reported to be a potential adverse outcome predictor in renal transplantation (rTp). We investigated whether non-adherence is associated with increased rTp graft rejection and/or failure in patients with LN.

Methods

Patients with LN undergoing rTp in two major London hospitals were retrospectively included. Medical and electronic records were reviewed for documented concerns of non-adherence as well as laboratory biochemical drug levels. The role of non-adherence and other potential predictors of graft rejection/failure including demographics, comorbidities, age at systemic lupus erythematosus and LN diagnosis, type of LN, time on dialysis prior to rTp and medication use were investigated using logistic regression.

Results

Out of 361 patients with LN, 40 had rTp. During a median follow-up of 8.7 years, 17/40 (42.5%) of these patients had evidence of non-adherence. A total of 12 (30.0%) patients experienced graft rejection or failure or both. In the adherent group 2/23 (8.7%) had graft rejection, whilst in the non-adherent this rose to 5/17 (29.4%, $p = 0.11$). Graft failure was seen in 5/23 (21.7%) patients from the adherent group and 4/17 (23.5%) in the non-adherent group ($p = 0.89$). Non-adherent patients had a trend towards increased graft rejection, hazard ratio 4.38, 95% confidence interval = 0.73–26.12, $p = 0.11$. Patients who spent more time on dialysis prior to rTp were more likely to be adherent to medication, $p = 0.01$.

Conclusion

Poor adherence to immunosuppressive therapy is common and has been shown to associate with a trend towards increased graft failure in patients with LN requiring rTp. This is the first paper to report that shorter periods on dialysis prior to transplantation might lead to increased non-adherence in lupus patients.

Introduction

According to the World Health Organization medication adherence is “the extent to which a person's behaviour (taking medications, following a recommended diet and/or executing lifestyle changes) corresponds with the agreed recommendations of a health care provider”.[1] We and others have shown that adherence to medication is variable in patients with systemic lupus erythematosus (SLE), with poor adherence often affecting more than 50% of the patients; this might potentially be associated with worse overall prognosis.[2–4]

Renal transplantation (rTp) for patients with lupus nephritis (LN) is an increasingly utilized therapy for end stage renal disease.[5,6] However, the sparsity of suitable donors and frequent allosensitization of lupus patients due to receipt of blood products and prior pregnancies mean that most patients spend significant time on dialysis before transplantation. Poor adherence to immunosuppressive therapy has been shown to be associated with increased graft failure in renal transplant patients. Up to 16% of graft losses are attributed, in part, to poor adherence.[7,8]

It is recognized that in patients with rTp non-adherence can lead to acute and chronic rejection, reduced renal function potentially necessitating return to dialysis and even death.[9] Returning to dialysis after a failed renal transplant is associated with a 78% mortality risk compared to patients on the transplant waiting list receiving dialysis.[10] However, despite the available evidence linking non-adherence to adverse outcomes in patients with transplantation, little is known regarding adherence in patients with LN following rTp and whether less adherent patients have worse outcomes.

In this study we investigated potential factors leading to non-adherence in patients with SLE who underwent rTp for LN and whether evidence of non-adherence associates with increased renal graft rejection, defined as an acute deterioration in the graft function associated with specific histopathological changes in the graft; or with failure, defined as the need for dialysis or re-transplantation.

Methods

All patients with diagnoses of both SLE and renal failure leading to rTp from two major London hospitals (University College London Hospital and Royal Free

Hospital) since 1975 were retrospectively identified and included in this study analyzing prospectively captured data. All patients fulfilled ≥ 4 of the 1982 revised classification criteria for SLE of the American College of Rheumatology[11] and we used the International Society of Nephrology/Renal Pathology Society 2003 classification system to define the histological class of LN.[12] Patients receiving a transplant prior to 1982 were retrospectively shown to fulfil the 1982 criteria.

We retrospectively reviewed hospital electronic and paper records and correspondence with family practitioners and with other hospital physicians to identify any documented concerns about non-adherence to prescribed immunosuppressive treatment. Such concerns would usually be documented if the patients volunteered that they were not adherent to the medication themselves, or the information came from family members or the patients admitted to this following direct questioning. Furthermore, in the United Kingdom repeat prescriptions are facilitated by the general practitioner looking after the patients in the community. Therefore, if the patients do not renew their prescriptions in the community, the general practitioner or the pharmacist will quickly become aware of this and will bring this to the attention of the clinical team for further evaluation. A recent article revealed that although patient reporting could detect even relatively infrequently missed tablets, drug monitoring could also identify severe non-adherence.[3] Thus, we also reviewed the trough blood levels recorded for patients on tacrolimus or ciclosporin and mycophenolate mofetil to help ascertain evidence of non-adherence. As there is no standard biochemical definition of non-adherence for patients with a renal transplant, we took a realistic and pragmatic approach of defining non-adherence as evidence of sub-therapeutic drug levels in routine measuring in >50% of the readings taken, at least 6 months after the rTp to avoid levels taken during the initial introduction of the medication and individual dose adjusting. We used the percentage of sub-therapeutic trough levels of immunosuppressant medication as a surrogate marker of poor adherence rather than trough level variability, as the former has been reported to be more strongly associated with graft rejection after kidney transplantation.[7] Finally, we examined potential associations with poor adherence including sex, ethnicity, age at SLE diagnosis, age at LN diagnosis, age when dialysis was started, duration of SLE diagnosis to LN, histological type of LN, time on dialysis prior to transplantation, and other existing conditions such as diabetes mellitus, hypertension, dyslipidaemia and prior cardiovascular disease. The

primary endpoint was renal graft rejection (defined as acute deterioration in graft function with rejection confirmed histopathologically) occurring > 12 months from the transplantation. Secondary endpoints included renal graft failure (defined as a need for dialysis or re-transplantation) and a composite endpoint of graft rejection and/or failure > 12 months from the transplant. As such, if graft failure was identified the patients were censored for the purposes of the secondary outcomes, but continued to be monitored for the primary endpoint of renal graft rejection in the second transplant. The study was a retrospective review of a long-term observational registry and, in effect, an audit for which University College London does not require formal ethical permission.

Statistical analysis

Categorical variables are presented as number and percentage whilst continuous variables are presented as mean and standard deviation (if normally distributed) or otherwise median and interquartile range. Comparisons between groups were performed using Student's *t*-test for normally distributed data or the Mann–Whitney *U* test for other data or Fisher's exact test. Logistic regression was used to investigate the potential association between non-adherence and renal graft rejection or failure. A $p < 0.05$ was considered significant. IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

Three hundred and sixty-one patients with SLE were identified with LN, the vast majority biopsy confirmed (>90%), of whom 40 had rTp for LN. A total of 17/40 (42.5%) patients were identified to be non-adherent to prescribed treatment for LN (Figure 1).

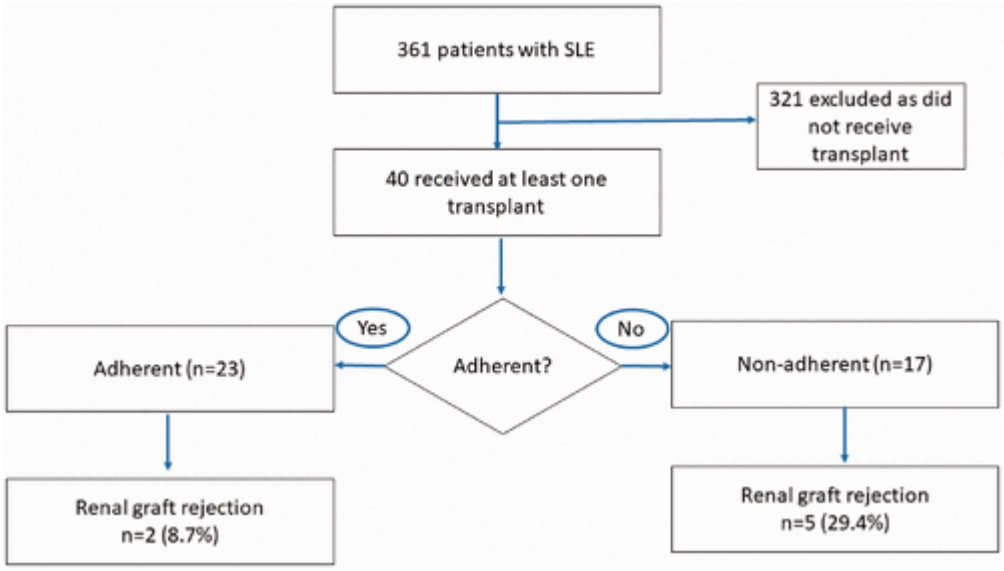

Figure 1 Flow diagram indicating the study population included in this cohort.

SLE: systemic lupus erythematosus.

As shown in Table 1, the only significant difference between the adherent and non-adherent groups was the amount of time spent on dialysis with the adherent group spending 33 (27–79) months on dialysis versus the non-adherent group spending 17 (10–24) months on dialysis, $p = 0.01$. There were no other significant differences in adherent and non-adherent patients. In particular, in this cohort there was no difference between the groups with regards to the age at SLE diagnosis or rTp, gender, ethnicity, diagnosis duration, medication prescribed or donor source. In addition, there were no significant differences in other comorbidities between the two groups as shown in Table 1 (all values $p > 0.05$). Furthermore, there was no difference in adherence versus non-adherence patterns in patients who had received rTp prior to the year 2000 or after this time. Moreover, there was no difference in the group that had ever received azathioprine or ciclosporin, compared to the group that had never received either of these medications in terms of adherence (all values $p > 0.05$). This would support the assumption that even if immunotherapeutic regimes were modified during the period of the study, this was unlikely to affect the pattern of adherence/non-adherence.

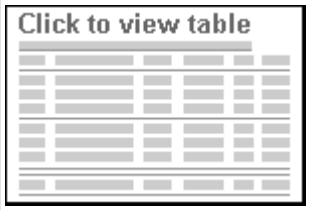

Table 1 Patient demographic comparison between adherent and non-adherent groups

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	Adherence (n = 23)	*Non-adherence (n = 17)*	p *value*
Sex/female	20 (87%)	14 (82%)	0.70
Ethnicity			0.51
Caucasian	8	9	
Afro-Caribbean	10	5	
Asian	5	3	
Age at SLE diagnosis (years)	22 ± 9	21 ± 11	0.55
Age at LN (years)	27 ± 8	26 ± 9	0.63
Time on dialysis (months)	33 (27–79)	17 (10–24)	0.01
DM	2 (9%)	0 (0%)	0.50
HTN	3 (13%)	6 (35%)	0.12
Dyslipidaemia	3 (13%)	1 (6%)	0.62
APLS	2 (9%)	2 (12%)	0.76
CVS	2 (9%)	3 (18%)	0.43
Histology type IV	9 (39%)	6 (35%)	0.55
Donor living	8 (35%)	10 (59%)	0.20
rTp time			0.41
Before year 2000	6 (26%)	2 (12%)	
After year 2000	17 (74%)	15 (88%)	
Age of ESRD (years)	30 ± 9	32 ± 12	0.59
Age at rTp (years)	36 ± 11	34 ± 12	0.57
Graft rejection	2 (9%)	5 (29%)	0.11
Graft failure	5 (22%)	4 (24%)	0.89
Rejection or failure	5 (22%)	7 (41%)	0.21

Figures represented are mean ± SD, median (interquartile range), frequency, and frequency (percentage).
APLS: antiphospholipid antibody syndrome; CVS: cardiovascular disease; DM: diabetes mellitus; ESRD: end stage renal disease; HTN: hypertension; LN: lupus nephritis; rTp: renal transplantation; SLE: systemic lupus erythematosus.

One patient received three rTps in total and had a rejection on the initial transplant. Two more patients received two rTps each. One had rejection on the initial graft whilst the second one did not have evidence of rejection either on the first or second graft.

Recording a concern about non-adherence, either following medical consultation or biochemically, supported a trend to increased graft rejection. During a median follow-up of 8.7 years, 17/40 (42.5%) of patients had evidence of non-adherence (Table 1). A total of 12 (30.0%) patients experienced graft rejection or failure or both. From the adherent group 2/23 (8.7%) had graft rejection whilst from the non-adherent group this was 5/17 (29.4%, $p = 0.11$). Graft failure was seen in 5/23 (21.7%) patients from the adherent group and 4/17 (23.5%) in the non-adherent group ($p = 0.89$). Using logistic regression, non-adherent patients had a trend towards increased renal graft rejection (hazard ratio 4.38, 95% confidence interval 0.73–26.12, $p = 0.11$). There were no significant predictors for graft rejection or failure or the composite endpoint of either of them as shown in Table 2. However, presence of class IV LN on pre-transplant histology had a trend towards a greater risk of graft rejection/failure ($p = 0.06$).

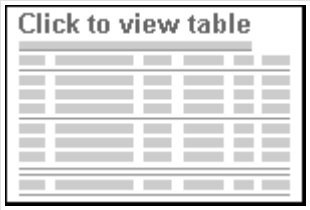

Table 2 Logistic regression hazard modelling investigating non-adherence and other potential predictors and graft failure

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	Hazard Ratio	*95% Confidence Interval*	*P-value*
Gender male			
Rejection	–		
Failure	0.65	0.07–6.41	0.65
Rejection or Failure	0.42	0.04–4.02	0.45
Ethnicity			
Rejection	0.76	0.33–1.73	0.50
Failure	0.70	0.27–1.81	0.46
Rejection or Failure	0.60	0.26–1.36	0.22
Age at SLE Diagnosis			
Rejection	1.02	0.95–1.09	0.65
Failure	1.06	0.98–1.16	0.16
Rejection or Failure	1.05	0.97–1.13	0.24
Age at LN			
Rejection	0.98	0.88–1.09	0.70
Failure	1.03	0.94–1.13	0.48
Rejection or Failure	1.02	0.94–1.11	0.63
Age starting dialysis			
Rejection	1.04	0.97–1.12	0.29
Failure	1.05	0.98–1.13	0.17
Rejection or Failure	1.04	0.98–1.12	0.21
Time on dialysis			
Rejection	1.00	0.98–1.02	0.87
Failure	1.00	0.99–1.02	0.86
Rejection or Failure	1.00	0.99–1.01	0.83
DM			
Rejection	–		
Failure	3.33	0.18–61.69	0.42
Rejection or Failure	2.25	0.12–40.66	0.58
HTN			
Rejection	2.50	0.39–16.05	0.33
Failure	1.75	0.30–10.34	0.54
Rejection or Failure	2.09	0.39–11.06	0.39
Dyslipidaemia			
Rejection	1.20	0.10–14.19	0.89
Failure	3.60	0.40–32.37	0.25
Rejection or Failure	2.29	0.27–19.66	0.45
APLS			
Rejection	1.13	0.10–13.44	0.92
Failure	0.89	0.08–13.30	0.93
Rejection or Failure	2.14	0.25–18.50	0.49
CVS history			
Rejection	–		
Failure	2.00	0.26–15.62	0.51
Rejection or Failure	1.24	0.17–9.25	0.84
Histology type IV			
Rejection	–		
Failure	7.00	0.65–75.74	0.11
Rejection or Failure	9.80	0.90–106.85	0.06
Donor source			
Rejection	1.62	0.31–8.48	0.57
Failure	1.54	0.34–6.93	0.58
Rejection or Failure	1.91	0.48–7.64	0.36
Non-adherence			
Rejection	4.38	0.73–26.12	0.11
Failure	1.11	0.25–4.94	0.89
Rejection or Failure	2.52	0.63–10.05	0.19

Where a (–) is present it indicates too few events in that group to allow statistical modelling.

APLS: antiphospholipid antibody syndrome; CVS: cardiovascular disease; DM: diabetes mellitus; HTN: hypertension; LN: lupus nephritis; SLE: systemic lupus erythematosus.

Interestingly, a longer time on dialysis prior to the transplantation was associated with decreased non-adherence. For every additional month on dialysis non-adherence was reduced by hazard ratio 0.96, 95% confidence interval 0.93–0.99, $p = 0.02$. A receiver operating characteristic curve (Figure 2) identified that spending more than 25 months on dialysis was more likely to lead to better adherence with sensitivity 0.77, specificity 0.82 and good discrimination with area under the curve=0.76, supporting the idea that patients who spend more time on dialysis are more likely to be more adherent, and thus those with less time spent on dialysis prior to transplantation are more likely to become non-adherent.

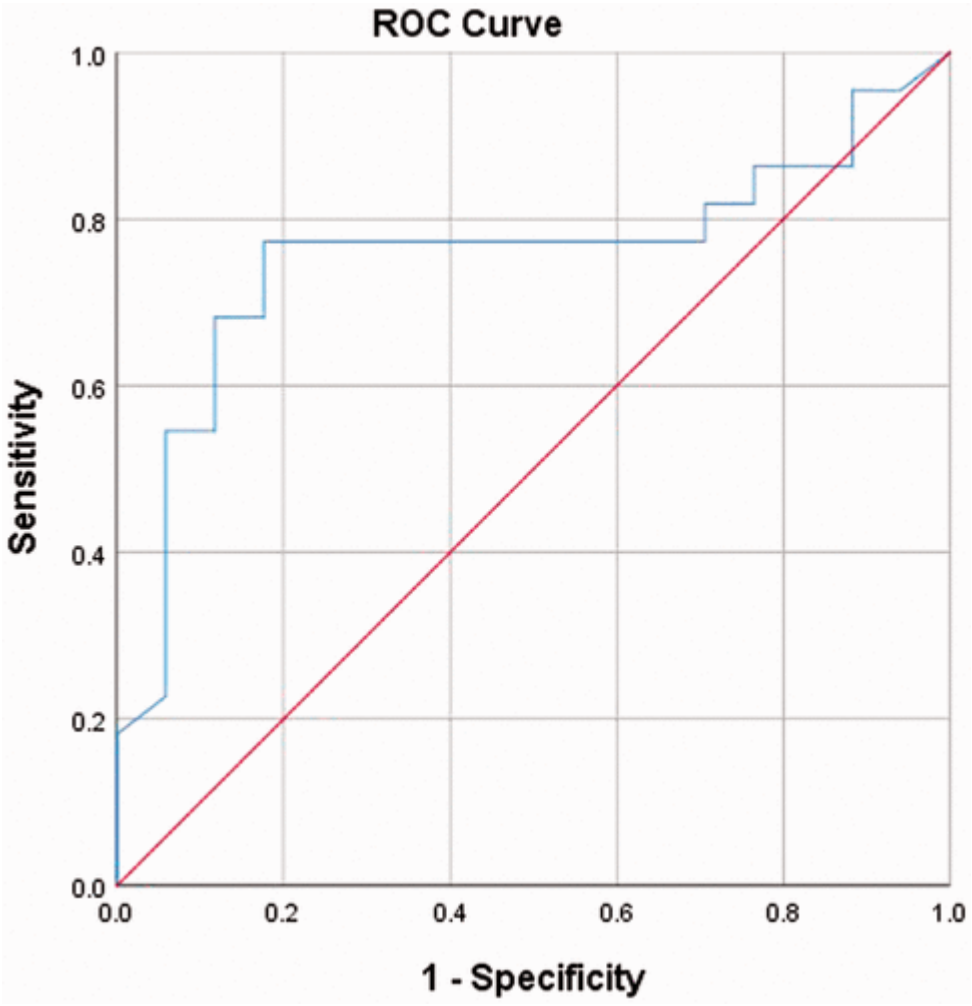

Figure 2 Receiver operating characteristic (ROC) curve indicating that dialysis time of more than 25 months prior to renal transplantation was associated with improved adherence (sensitivity 0.77, specificity 0.82 and good discrimination with area under the curve = 0.76).

Discussion

In this study we considered the role of adherence to immunosuppressive treatment in patients with LN requiring rTp. We documented, for the first time, adherence patterns specifically for this cohort of patients and also investigated whether non-adherence was associated with an increased risk of graft rejection and/or failure. Our results confirmed that more than 2/5 of our patients with LN, even after rTp, were considered to be non-adherent, either based on medical record evidence or based biochemically on drug level testing.

What is particularly noteworthy is that once a concern about non-adherence was documented either in the medical notes or as evidenced with biochemical assays, there was a trend to more than a four-fold higher risk of graft rejection, indicating that poor adherence could have potentially significant adverse effects.

As this was an observational retrospective study, it was not possible to investigate causality leading to non-adherence. However, our results raise the strong possibility that patients who spend more time on dialysis are, in fact, more adherent to medication following transplantation. This is an important novel finding, as it may suggest that the time spent on dialysis has an indirect effect in encouraging better adherence post-transplant, perhaps because patients are more motivated to avoid returning to dialysis. With an increasing number of pre-emptive transplantation[6,13] it is possible that non-adherence could also increase, and therefore the clinicians and other health care professionals should be aware and ever vigilant in recognizing this. We have recently shown that increasing time on dialysis prior to rTp adversely affects prognosis specifically in lupus patients,[14] supporting previous literature in patients with renal disease of mixed aetiology receiving rTp,[15] and therefore minimizing the time on dialysis should remain the aim. However, particular attention should be paid to the patients who spent little or no time on dialysis to ensure that non-adherence does not compromise the beneficial effects of early transplantation.

Limitations

Although we included patients from two large hospitals in London over a four-decade period, we were only able to identify 40 eligible transplanted patients from an original cohort of 361 patients. This number, although modest, is in line with or

larger than other similar published studies of LN.[16,17] Our study was retrospective; however, we endeavoured to avoid any bias by only considering strong pre-defined surrogates for non-adherence, such as clear documentation in the notes about poor adherence, or biochemical markers of non-adherence, and a well-defined endpoint of graft rejection and failure.

Moreover, we had a mixture of Caucasian, Afro-Caribbean and Asian patients and therefore our study results cannot be extrapolated to other populations. In view of this and also the relatively modest numbers in this study, we might have been underpowered to detect small but significant differences specific to individual ethnicity. As we focused our research only in the LN renal transplant patients, we are not able to comment about whether adherence in this cohort is higher or lower than the patients remaining on dialysis. In addition, the retrospective nature of the study did not allow us to screen accurately for depression, a factor known to be associated with non-adherence in the general lupus population.[18] Finally, despite one of the longest recorded follow-up periods exceeding 422 patient-years, we only had 12 patients with graft rejection or failure, which may have impacted on identifying smaller potential associations with the other variables included in this study.

Conclusion

In conclusion, this study with a notably long-term follow-up has shown that poor adherence persists in patients with LN even after rTp. It further shows that poor adherence may be associated with worse renal graft rejection and that shorter periods on dialysis prior to transplantation might lead to increased non-adherence. This is the first study to support such a conclusion. Further research needs to be undertaken collaboratively in multiple centres to identify the true adverse role of non-adherence in patients with renal transplant due to LN. Such studies can also investigate further the factors leading to poor adherence in this cohort of patients.

Identifying patients at risk of non-adherence utilizing a combination of methods based on such factors is a key step. More importantly, patients at risk of or with documented concerns about adherence should be closely followed up with regular biochemical testing, and a purposeful discussion about the likely consequences of non-adherence in the outpatient clinics may be necessary. Finally, enhanced

education sessions highlighting the importance of immunosuppressive therapy adherence could be considered for all the lupus patients following rTp but also importantly in anticipation of rTp.

Key messages

- Non-adherence to immunosuppressive medication following renal transplantation in patients with lupus nephritis is common
- Non-adherence might lead to increased graft rejection following renal transplantation for lupus nephritis
- Longer periods on dialysis prior to renal transplantation are associated with improved adherence post-transplantation

Author contribution

EN planned the study, obtained funding, collected data and drafted the manuscript; VSV performed the statistical analysis and provided significant revisions to the manuscript; AVG collected data and provided significant revisions to manuscript; ADS planned the study, obtained funding, collected data and drafted the manuscript; DAI planned the study, obtained funding, collected data and drafted the manuscript.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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