

Follow-Up Factors Contribute to Immunosuppressant Adherence in Kidney Transplant Recipients

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Purpose: Follow-up and immunosuppressive medication (ISM) adherence are both important for kidney transplant recipients postoperatively and whether follow-up factors affect the ISM adherence remains unclear. The aim of this study was to examine the relationship between follow-up factors and ISM adherence, and the factors associated with ISM adherence.

Patients and Methods: An internet-based cross-sectional survey was conducted in a single kidney transplant center in China. The participants completed the internet-based questionnaire and the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS©) from January 12 to January 26, 2021.

Results: Finally, 288 (66.7%) participants responded to this survey. The percentage of full adherence to immunosuppressant was 51.7% (149/288), with 33.3% of the participants reporting a problem in timing dimension. We found that follow-up with a fixed doctor was significantly positive to good adherence (OR=2.124, 95% CI=1.111–4.062, $P=0.023$) after analyzing the survey data. Time since kidney transplantation and number of non-immunosuppressants were both associated with immunosuppressant adherence. No significant difference was found regarding the effect of the follow-up adherence on ISM adherence.

Conclusion: Our study demonstrated an insufficient prevalence of adherence to immunosuppressant in Chinese renal transplant recipients and revealed that follow-up with a fixed doctor may be a way to improve the patients' ISM adherence. This anonymous internet-based survey provides valuable insight into the actual adherence rate, factors associated with non-adherence, and situations that may improve medication-taking.

Keywords: immunosuppressive medication, medication adherence, follow-up, internet-based survey, kidney transplantation

Introduction

Immunosuppressive medication (ISM) non-adherence is one of the most important causes for shortened graft survival subsequently leading to a reduction in kidney graft survival results.¹ Kidney disease improving global outcomes (KDIGO) reported ISM non-adherence to be as high as 50% in developed countries, while non-adherence in developing countries might even be higher.¹

Various methods to evaluate the ISM adherence of kidney transplant recipients have been reported, which include questionnaires, immunosuppressive drug concentrations, pill counts or electronic pill-counting.² The scales were applied in many surveys for ISM adherence, in which paper questionnaires were used in almost all the studies. However, it was difficult to obtain the true adherence information as patients tend to conceal the truth in clinical settings as they are required have a face-to-face evaluation at the clinic.² This may be avoided by internet-based surveys with verified reliability, according to a study by Kobayashi et al.³

Risk factors for ISM non-adherence can be divided into modifiable and non-modifiable risk factors, which are of key importance when trying to resolve non-adherence. For example, age and sex are non-modifiable risk factors.¹ There are multiple factors that influence ISM adherence among patients after kidney transplantation, according to the present literature.^{3–14} Patient-related factors and therapy-related factors, including age, sex, quality-of-life, and post-transplantation time, were the main factors reported to be associated with immunosuppressant adherence.

With the exception of ISM non-adherence, kidney transplant patients are also reported to have follow-up non-adherence.¹⁵ This may also lead to medication non-adherence in patients. Follow-up adherence plays a vital role in the medical surveillance of the kidney transplant recipients. Zhao et al's¹⁶ study suggested that follow-up adherence of patients decreases with time after transplantation. In addition to adherence, follow-up physicians were another factor. However, rarely have studies explored the relationship between follow-up factors and ISM adherence.

We conducted an internet-based survey to investigate the immunosuppressant medications adherence among kidney transplant recipients in China. The aims of our study are two-fold: 1) to assess the prevalence of non-adherence in Chinese kidney transplant patients; and 2) to clarify the relationship of follow-up factors and ISM non-adherence, thus obtaining valuable information for the development of interventions to reduce non-adherence.

Materials and Methods

Sample Selection

The internet-based survey was conducted in China for 3 weeks in January 2021. The questionnaire was delivered to ten patients for preliminary experiments during the pre-experimental stage. It was then published in the kidney transplant recipient follow-up WeChat group after completing the adjustment of questionnaire. Patients who provided informed consent within the questionnaire participated in this survey. Patients who were unwilling to give informed consent were automatically excluded from this survey. All kidneys were donated voluntarily with written informed consent, and this was conducted in accordance with the Declaration of Istanbul. The inclusion criteria included: 1) kidney transplant recipients; 2) aged more than or equal to 18; 3) had the ability to read and understand Chinese; 4) time since transplantation >6 months; and 5) agreed to participate in the survey. We excluded patients with combined organ transplantation or who had a cognitive or sensory impairment (such as blindness or deafness) that prevented them from completing an interview. This study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of Zhongshan Hospital, Fudan University (No. B2020-228R).

Measurements

ISM Adherence

The Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS®),¹⁷ a self-reported questionnaire developed by the Leuven Basel Adherence Research Group, was used to evaluate the immunosuppressive medication adherence. Four items were contained in it for evaluating both the frequency and timing of medication intake, and one item for assessing discontinuation (stop medication intake completely). Cronbach's α for the total score in our study was 0.563.

Sociodemographic and Medical Characteristics

The following characteristics were recorded and analyzed in our study: age, sex, marital status (married vs single/divorced), whether first time renal transplantation or not, time since transplantation (≤ 1 year, 1–5 years, 5–10 years, ≥ 10 years), residence (rural vs urban), employment status (employed vs unemployed), educational status (middle school and below, high school, bachelor and above), healthcare insurance (Self-paying, New Rural Cooperative Medical Scheme (NRCMS), Urban Resident Basic Medical Insurance (URBMI)/Urban Employee Basic Medical Insurance (UEBMI)), self-report economic burden (free, mild, moderate, heavy), number of times taking medicines per day (≤ 3 , 3–5, >5), complications (diabetes mellitus, hypertension, hyperuricemia, hyperlipidemia, BK virus infection), and use of a medicine box (yes or no). Medication regimen complexity has been found to be one of the main reasons for non-adherence among kidney transplantations, as most of the patients need to take non-ISM for the treatment of comorbidity,

such as hypertension or hyperlipidemia. The number of combinations with non-ISM (0, 1–3, >3) was surveyed to evaluate the complexity of the medication regime.

Follow-up factors included adherence of follow-up and whether they have a regular doctor for follow-up or not. The transplant recipients were required to have a follow-up examination at least once a month for the first 6 months after transplantation according to the follow-up advice of our transplantation center. Follow-up adherence was evaluated based on their frequency of follow-up visits in the past 6 months, and participants with less than six follow-up visits were considered to be follow-up non-adherent as the lowest follow-up frequency for patients 6 months after kidney transplantation is once per month.

Statistics

Statistical analyses were conducted using the IBM SPSS Statistics 26.0 software. Patients with at least one point in any of the five items (taking, skipping, timing, dose reduction, completely discontinued) were judged as non-adherent, according to the original BAASIS© criterion. Descriptive statistics and frequencies were obtained for the study variables.

In the univariate analysis, the *t*-test was performed for continuous variables, and the χ^2 test or Fisher's exact test were used for categorical variables. Statistical significance was set at $p < 0.05$. In addition, logistic regression analysis was conducted in multivariate analysis. All variables at $p < 0.25$ in univariate analysis were included in a multivariate analysis. Statistical significance was set at $p < 0.05$.

Results

Population Characteristics

Among the 432 respondents, 288 (66.7%) responded completely. Detailed characteristics are presented in Table 1, extracted from the 288 questionnaires. The mean age was 42.7 ± 10.3 years and more men (193/288, 67.0%) participated than women. Over 75% of the participants were more than 1 year after transplantation. Slightly over half of the patients participated in work regularly. More than a third of the participants had an undergraduate education background (171/276, 62%).

Table 1 Basic Characteristics of the Study Population and Differences Regarding Adherence to Immunosuppressants

Variables	Categories	Total (n (%))	Non-Adherent (n (%))	Adherent (n (%))	P-value [#]
Age (years) Mean (SD)		42.7 (10.3)	42.5 (9.6)	42.8 (10.9)	0.777
Sex	Female	95 (33.0)	47 (33.8)	48 (32.2)	0.803
	Male	193 (67.0)	92 (66.2)	101 (67.8)	
Secondary kidney transplantation		275 (95.5)	131 (94.2)	144 (96.6)	0.243
Time since transplantation (years)	≤1	61 (21.2)	15 (10.8)	46 (30.9)	<0.001
	1–5	128 (44.4)	66 (47.5)	62 (41.6)	
	5–10	48 (16.7)	24 (17.3)	24 (16.1)	
	≥10	51 (17.7)	34 (24.5)	17 (11.4)	
Employment status	Employed	154 (53.5)	86 (61.9)	68 (45.6)	0.004
	Unemployed	134 (46.5)	53 (38.1)	81 (54.4)	
Residence	Rural	55 (19.1)	25 (18.0)	30 (20.1)	0.377
	Urban	233 (80.9)	114 (82.0)	119 (79.9)	
Education	Middle school and below	41 (14.2)	19 (13.7)	22 (14.8)	0.513
	High school	135 (46.9)	70 (50.4)	65 (43.6)	
	Bachelor and above	112 (38.9)	50 (36.0)	62 (41.6)	
Marital status	Single/divorce	79 (27.4)	35 (25.2)	44 (29.5)	0.244
	Married	209 (72.6)	104 (74.8)	105 (70.5)	
Insurance	Self-paying	10 (3.5)	6 (4.3)	4 (2.7)	0.572
	NRCMS	33 (11.5)	18 (12.9)	15 (10.1)	
	URBMI/UEBMI	245 (85.1)	115 (82.7)	130 (87.2)	

(Continued)

Table 1 (Continued).

Variables	Categories	Total (n (%))	Non-Adherent (n (%))	Adherent (n (%))	P-value [#]
Economic burden	Free	36 (12.5)	17 (12.2)	19 (12.8)	0.478
	Mild	92 (31.9)	40 (28.8)	52 (34.9)	
	Moderate	96 (33.3)	46 (33.1)	50 (33.6)	
	Heavy	64 (22.2)	36 (25.9)	28 (18.8)	
ISM	Tacrolimus/MPA/Pred	212 (73.6)	101 (72.7)	111 (74.5)	0.475
	CsA/MPA/Pred	49 (17.0)	27 (19.4)	22 (14.8)	
	Others	27 (9.4)	11 (7.9)	16 (10.7)	
Diabetes		29 (10.1)	18 (12.9)	11 (7.4)	0.085
Hypertension		167 (58.0)	82 (59.0)	85 (57.0)	0.415
Hyperuricemia		100 (34.7)	56 (40.3)	44 (29.5)	0.036
Hyperlipemia		70 (24.3)	43 (30.9)	27 (18.1)	0.008
BKV viruria		28 (9.7)	11 (7.9)	17 (11.4)	0.212
No. non-ISA medications (n)	0	36 (12.5)	23 (16.5)	13 (8.7)	0.096
	1–3	167 (58.0)	80 (57.6)	87 (58.4)	
	>3	85 (29.5)	36 (25.9)	49 (32.9)	
No. times for taking medicines per day (n)	≤3	147 (51.0)	69 (49.6)	78 (52.3)	0.754
	3–5	96 (33.3)	46 (33.1)	50 (33.6)	
	>5	45 (15.6)	24 (17.3)	21 (14.1)	
Use medicine box	No	79 (27.4)	39 (28.1)	40 (26.8)	0.461
	Yes	209 (72.6)	100 (71.9)	109 (73.2)	

Notes: [#]Performed as t-test for continuous variables, and Chi-square test or Fisher exact test for categorical variables.

Univariate analysis showed that the following factors were statistically different between the adherent group and the non-adherent group: time since transplantation, employment status, hyperuricemia, hyperlipemia.

Prevalence of Non-Adherence

The results of the BAASIS© responses are shown in [Table 2](#). As assessed by the BAASIS©, overall implementation immunosuppressant agent adherence was 51.7%, while 48.3% of the participants were defined as non-adherent.

Timing non-adherence (delay or advance greater than 2 h) was the most frequent issue (96/288, 33.3%), followed by taking non-adherence (forgetting), reported by 24.7% (71/288). Drug holidays (14/288, 4.8%), dose alterations (16/288, 5.6%) and persistent non-adherence (stopping immunosuppressants completely) were less frequently reported (9/288, 3.1%). In the past 4 weeks, the frequency of most non-adherence behaviors was just once.

Association Between Follow-Up Factors and ISM Adherence

Follow-up factors stratified by adherence are shown in [Table 3](#). Univariate analysis showed that having a fixed doctor for follow-up was significant difference between these two groups ($p < 0.001$). Follow-up adherence was shown with no statistical difference between the ISM adherence and ISM non-adherence group.

We further analyzed the relationship between each dimension of the BAASIS scale and follow-up factors, which are shown in [Figure 1](#).

We found that the fixed follow-up physicians were statistically different in dimensions 1A, 1B, 2, and 3, but not in dimension 4. In terms of follow-up adherence, statistical differences were found only in dimension 2, and no statistical significance was found in other dimensions.

Multivariate regression analyses were conducted to further identify the influence of follow-up factors to ISM non-adherence. We did not find an effect of follow-up adherence on ISM adherence by adjusting the confounders. However, follow-up with a fixed doctor was still significantly positive to adherence (OR=2.203, 95% CI=1.203–4.030) after adjusting the confounders, as indicated in [Figure 2](#).

Table 2 Prevalence of Adherence Measured with BAASIS©

Adherence Behavior in Previous 4 Weeks	n	%
1A. Taking no-adherence		
No	217	75.3
Yes	71	24.7
1B. Drug holidays		
No	274	95.1
Yes	14	4.8
2. Timing no-adherence		
No	192	66.7
Yes	96	33.3
3. Dose alterations		
No	272	94.4
Yes	16	5.6
4. Discontinuation		
No	279	96.9
Yes	9	3.1
Total number categorized as showing no-adherence[†]	139	48.3

Notes: [†]Sum of participants answering affirmatively to 1A, 1B, 2, 3, and 4.

Table 3 Follow-Up Factors Stratified by ISM Adherence

	Total	Non-Adherence	Adherence	P-value
With a fixed doctor for follow-up (n (%))				<0.001
No	70	48 (34.5)	22 (14.8)	
Yes	218	91 (65.5)	127 (85.2)	
Follow-up adherence				0.099
No	142	76 (54.7)	66 (44.3)	
Yes	146	63 (45.3)	83 (55.7)	

Discussion

There are two principal findings from our study. First, the prevalence of ISM adherence in Chinese renal transplant patients was insufficient. Second, follow-up with a fixed physician was significantly positive to ISM adherence.

Consistent with the previous studies in kidney transplant patients of foreign countries, the prevalence of ISM adherence in our research is comparable to the previous studies, but is slightly lower than a Chinese study, measured by BAASIS©.⁵ A possible reason for this difference was that our survey was conducted with internet-based questionnaires. A relatively higher rate of non-adherence could be observed as the anonymous and convenient environment. Consistent with previous studies, timing non-adherence contributed the most to ISM non-adherence.^{3,18,19} The overall prevalence of ISM non-adherence was substantial, calling for investment in performance of adherence-enhancing interventions in kidney transplant recipients.

An important finding in our study was that a significant positive correlation between good adherence and follow-up with a fixed doctor can be observed. The adherence has been doubled at least in the participants with a fixed follow-up doctor than those without. Patients may not choose a fixed doctor for long-term follow-up management after kidney transplantation. This is related to the doctor's irregular visit time and the patient's medical habits. However, our study revealed that the adherence has been doubled at least in the participants with a fixed follow-up doctor than those without.

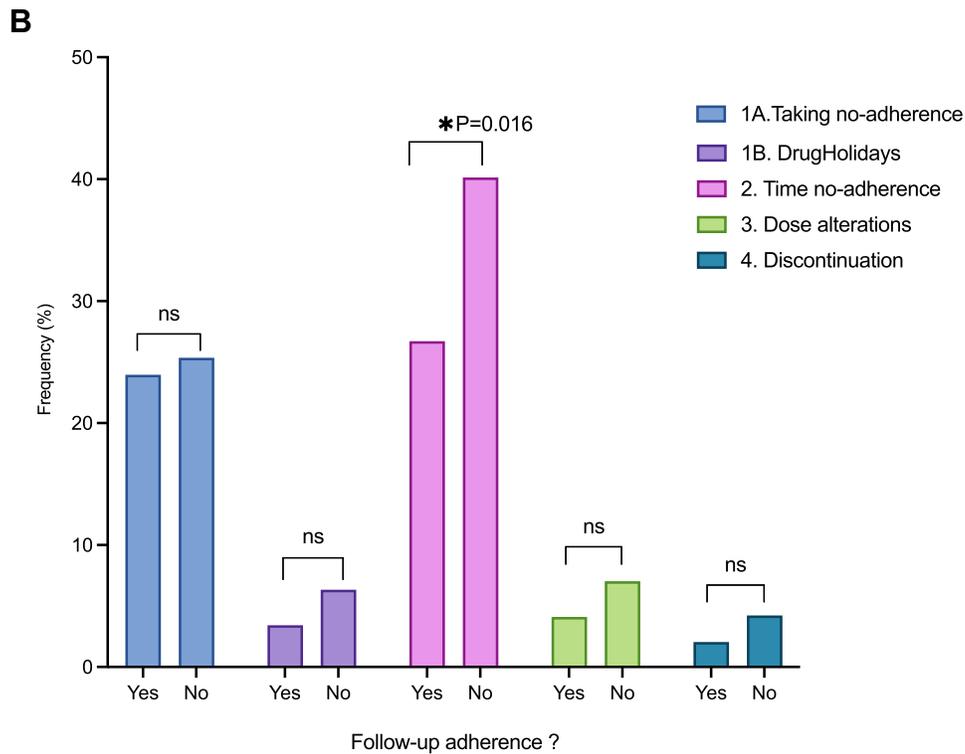
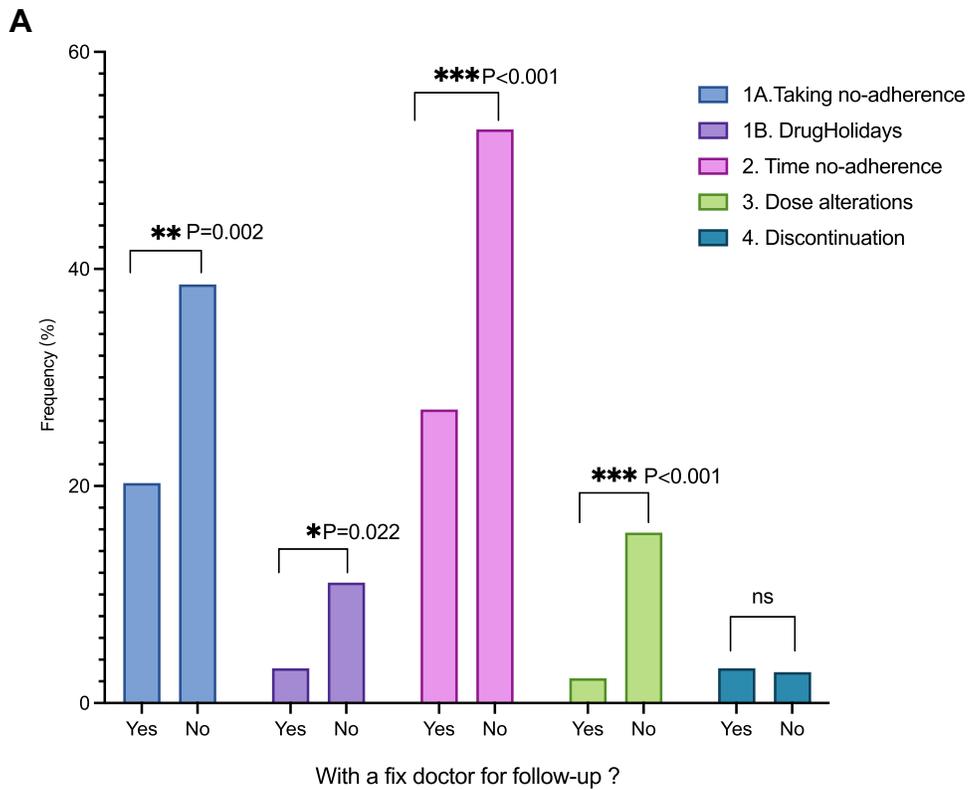


Figure 1 The relationship between each dimension of the BAASIS scale and follow-up factors. **(A)** Difference in fixed follow-up physicians between the adherence and non-adherence group; **(B)** Difference in follow-up adherence between the adherence and non-adherence group. *P<0.05; **P<0.01; ***P<0.001.

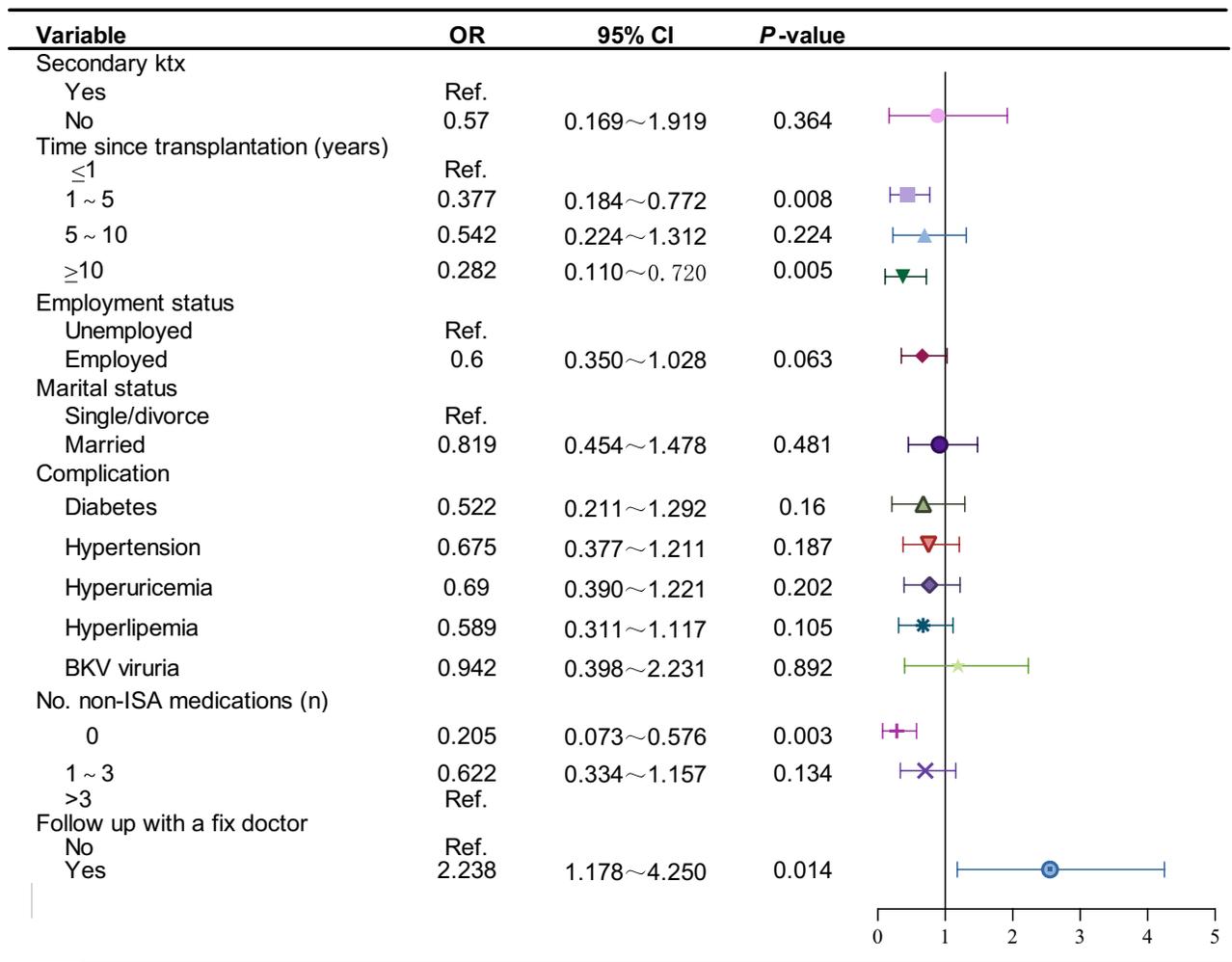


Figure 2 Factors associated with immunosuppressant medication adherence.

Follow-up with the same physician may facilitate communication, increase trust between physicians and patients, and help physicians keep abreast of patients' non-adherence behaviors. According to the study by Kobayashi et al,³ absence of medical staff for consultation after forgetting to take medication was associated with ISM non-adherence, while this low satisfaction might be avoided by following up with the same doctor due to the good communication between physician and patients. Fortunately, choice of follow-up physician is a modifiable factor for medication adherence barrier. So, our finding may help remind patients to choose a fixed follow-up physician for long-term follow-up after kidney transplantation. To our knowledge, this is the first time to investigate the effect of a fixed follow-up physician on immunosuppressant compliance.

Follow-up adherence was as high as another study in Chinese kidney transplantations by Zhao et al.¹⁶ Contrary to our hypothesis, no significant association was found between follow-up adherence and ISM adherence. This result may to some extent be in line with the study by Ng et al,¹⁵ which suggested that the at-risk population for one domain of non-adherence may not be the same as those at risk for other non-adherence behaviors. Zhao et al's study revealed that time after kidney transplantation was a factor affecting patient's adherence to follow-up, the longer the time after transplantation, the poorer the adherence to follow-up. Nevertheless, post-transplantation time is also related with ISM adherence, as indicated by both previous studies and our study. In addition, follow-up adherence may be overestimated as it is only evaluated in terms of frequency of follow-up visit. These two may also be factors affecting this study.

Multidrug combinations are often unavoidable in kidney transplant patients. Number of non-ISM used in combination was associated with ISM adherence, after adjusting for confounders. This was in accordance with some previous studies.²⁰ Our research suggested that ISM adherence was significantly lower in those who took more than three non-ISM compared to those who did not take additional non-ISM.

Our study has several limitations. First, it may be underrepresented for older people, people with visual impairments and those who do not use WeChat, as the study was conducted based on the internet. Second, participants selection was not randomized but convenience sampling, which can cause selection bias. Third, the sample size was too small to enable more extensive statistical analysis. In addition, we want to point out that the Cronbach's alpha for the BAASIS© was quite low. One possible reason for the low Cronbach's alpha is the fact that the BAASIS© consists only of five questions. Results (Cronbach's alpha 0.39–0.78) have been found in other adherence studies.^{9,19,21,22} Nevertheless, given the anonymous and convenience investigation method, it can still indicate an insufficient prevalence of immunosuppressant adherence in Chinese kidney transplant recipients, and reveal the importance of follow-up factors in immunosuppressant agents adherence.

Conclusion

In summary, this study provides a valuable viewpoint into the actual situation of immunosuppressant adherence in Chinese renal transplant recipients. Follow-up factors associated with ISM adherence were explored for further improving the ISM adherence. It is necessary to verify these findings in larger scale studies in the future.

Abbreviations

BAASIS, Basel Assessment of Adherence to Immunosuppressive Medication Scale; BKV, BK virus; CsA, cyclosporin; ISM, Immunosuppressive medication; KDIGO, Kidney disease improving global outcomes; MPA, mycophenolic acid; NRCMS, New Rural Cooperative Medical Scheme; Pred, prednisone; UEBMI, Urban Employee Basic Medical Insurance; URBMI, Urban Resident Basic Medical Insurance.

Disclosure

The authors report no conflicts of interest in this work.

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