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ORIGINAL ARTICLE

Describing the evolution of medication nonadherence from pretransplant until 3 years post-transplant and determining pretransplant medication nonadherence as risk factor for post-transplant nonadherence to immunosuppressives: The Swiss Transplant Cohort Study

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Conflicts of interest
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Summary

Although medication nonadherence (MNA) is a major risk factor for poor outcomes, the evolution of MNA from pre- to 3 years post-transplant among the four major organ transplant groups remains unknown. Therefore, this study described this evolution and investigated whether pretransplant MNA predicts post-transplant immunosuppressive medication nonadherence (IMNA). Adult participants (single transplant, pretransplant and ≤1 post-transplant assessment, using medications pretransplant) in the Swiss Transplant Cohort Study (a prospective nation-wide cohort study) were included. Nonadherence, defined as any deviation from dosing schedule, was assessed using two self-report questions pretransplant and at 6, 12, 24 and 36 months post-transplant. Nonadherence patterns were modelled using generalized estimating equations. The sample included 1505 patients (average age: 52.5 years (SD: 13.1); 36.3% females; 924 renal, 274 liver, 181 lung, 126 heart). The magnitude and variability of self-reported MNA decreased significantly from pretransplant to 6 months post-transplant (OR = 0.21; 95% CI: 0.16–0.27). Post-transplant IMNA increased continuously from 6 months to 3 years post-transplant (OR = 2.75; 95% CI: 1.97–3.85). Pretransplant MNA was associated with threefold higher odds of post-transplant IMNA (OR = 3.10; 95% CI: 2.29–4.21). As pretransplant MNA predicted post-transplant IMNA and a continuous increase in post-transplant IMNA was observed, early adherence-supporting interventions are indispensible.

Introduction

Immunosuppressive medication nonadherence (IMNA) is highly prevalent in solid organ transplant recipients [1]. A meta-analysis showed that, among solid organ transplant recipients, 22.6 cases per 100 persons per year are nonadherent to immunosuppressive drugs. Considerable variability was observed among organ groups: kidney recipients had the highest rate (35.6 cases per 100 persons per year), followed by heart recipients (14.5 cases per 100 persons per year); liver transplant recipients had the lowest rate (6.7 cases per 100 persons per year) [1].

Immunosuppressive medication nonadherence is a major risk factor for poor clinical and economic outcomes in solid organ transplant recipients: research on renal transplant recipients, the group for whom the most evidence on

IMNA is available–[2] has linked it to acute rejection episodes, graft loss, reduced renal function and increased healthcare costs [2]. Over a 5-year prospective study, Vlaminck *et al.* [3] observed that nonadherent renal transplant patients suffered accelerated declines in kidney function, while Butler *et al.* [4] showed that 36% of graft failures were IMNA-related. From a subclinical perspective, Butler *et al.* showed a sevenfold likelihood (95% CI: 4–12; $P < 0.001$) of graft failure in nonadherent recipients than in the adherent group. The resulting clinical outcomes entail a heavy financial burden: a US study showed that, on average, in the first 3 years following transplantation, nonadherent renal transplant patients' medical costs exceeded those of the adherent by USD 21 600 [5].

Therefore, IMNA emerges as a relevant behavioural parameter to be considered in the transplant selection process [6,7]. Moreover, identifying patients at risk for IMNA as early as possible and targeting them for interventions is essential, especially in light of Dobbels *et al.*'s [8] study of heart, lung and liver recipients, which showed that pretransplant medication nonadherence (MNA) predicts posttransplant IMNA in the 1st year post-transplant. However, determining the optimal moment to initiate adherence enhancing interventions requires an understanding of the evolution of medication nonadherence in all four solid organ transplant groups over the pre- to post-transplant course. To date, while limited prospective studies have described the development of MNA [1,9–12], the present study is the first to examine all four major organ transplant groups concurrently while also assessing pretransplant MNA.

The Swiss Transplant Cohort Study (STCS), a nationwide prospective cohort study, provides a valuable research framework to study the evolution of medication nonadherence both across and within the four main solid organ transplant groups from pretransplant to end of life posttransplant [13]. Begun in May 2008, the STCS tracks all solid organ transplant patients who receive transplants in Switzerland from pre- to post-transplant, gathering data on outcome-linked factors including pre- and post-transplant MNA and IMNA [13,14].

The aims of this study were therefore as follow: (i) to prospectively describe the evolution of MNA from pretransplant until 3 years post-transplant in liver, renal, lung and heart transplant recipients; and (ii) to determine whether pre-transplant MNA is predictive of post-transplant IMNA.

Materials and methods

Design/sample and setting

This study used data from the STCS, a prospective nationwide cohort study including all patients transplanted in the six Swiss transplant centres. The design of the STCS has been documented elsewhere [13,14]. At the time of each transplant candidate's (pretransplant) STCS inclusion, selected socio-demographic, psychosocial and behavioural variables – including medication adherence – are collected via the STCS's Psychosocial Questionnaire (PSQ). Follow-up data are collected 6 months post-transplant, 1 year post-transplant and each year thereafter [13,14]. The current study used STCS data from kidney, liver, lung and heart transplant patients enrolled in the STCS from 2 May, 2008 until 21 August, 2013. Additional inclusion criteria were: single transplant, 18 years of age or older, the existence of a pretransplant PSQ assessment for medication adherence, and taking medications pretransplant.

Variables and measurement

Socio-demographic and clinical variables

Variables extracted from the STCS database for use in this analysis included gender, age in years at the time of transplantation, transplanted organ (kidney, liver, heart, lung), date of transplantation, highest completed educational degree and marital status (single, married/living together, widow/widower, divorced, separated, answer refused). Marital status was dichotomized as either living alone (single, widow/widower, divorced, separated) or not living alone (married/living together). Depressive symptomatology was assessed using the 7-item depression scale of the Hospital Anxiety and Depression Scale. The items are scored from 0 to 3 and the total score calculated by summing the seven items' scores (total score range: 0–21) [14,15].

Medication adherence

Medication adherence was assessed using two self-report items derived from the BAASIS© instrument, assessing two dimensions of medication adherence, i.e., taking adherence and drug holidays [16]. As the BAASIS© was developed specifically to assess IMNA in solid organ transplant recipients [16], the STCS uses its items unmodified to gather post-transplant IMNA data. However, relevant items have also been adapted to measure pretransplant MNA. Asked "How often did you miss a dose of medication (pretransplant)/immunosuppressive medication (post-transplant) in the past 4 weeks?" patients indicated their responses on a 6-point Likert-type scale ('Every day', 'More than once a week', 'Once a week', 'Once every 2 weeks', 'Once a month' or 'Never'). A second item assessed the frequency of drug holidays. These were assessed as following: patients were asked "Did you miss more than one consecutive dose of your (immunosuppressive) medication in the past 4 weeks?" ('yes'/'no') [14]. A positive outcome of MNA and IMNA was defined as any missed doses; having missed

at least one dose of medication and/or having missed two or more consecutive doses over the past 4 weeks.

Concurrent validity of the BAASIS© self-report items has been demonstrated in a Brazilian kidney transplant sample [17]. Predictive validity was established in a study in liver transplant recipients which demonstrated that IMNA (as assessed by the BAASIS©) was predictive of the 5-year incidence of late acute rejection [18]. Predictive validity has also been established in the Swiss HIV cohort study [19,20], where missed doses from the taking adherence dimension showed a linear relationship with optimal viral suppression [19]. Other work in HIV patients supports these items' validity relative to electronic monitoring [21], and predictive validity of the taking adherence item was also indicated in a large hypertension study [22].

Importantly, Switzerland has no easily accessible database of pharmacy refill records, the STCS includes no information on assays of immunosuppressive drugs, and electronic monitoring is too complex and expensive to be integrated into such a large and lengthy study; therefore, self-reporting was the only medication nonadherence assessment method feasible for the STCS (see also Discussion section) [23].

Data collection

Swiss Transplant Cohort Study data collection includes biomedical, genetic, psychosocial and behavioural variables [13,14]. Since May 2008, all patients, evaluated and waitlisted for transplantation in Switzerland have been invited to participate in the STCS, along with any patients already on transplant waiting lists. After providing written informed consent, patients complete the pretransplant PSQ. After transplantation, each participant is sent the PSQ to complete at a designated data collection point. PSQ completeness is checked by local STCS data managers, after which data are entered into the central database. Further details on STCS data collection have been published elsewhere [13,14].

Analysis

Descriptive statistics included frequencies, proportions, and measures of central tendency (mean, median) and dispersion (standard deviation, interquartile range) as appropriate based on measurement level and distribution.

To test the magnitude and evolution of nonadherence from pretransplant until 3 years post-transplant, logistic regression was used, with parameters estimated via generalized estimating equations (GEE) – a widely-used method of adjusting for lack of independence in longitudinal data collected via repeated measurement [24]. As the STCS is an open cohort, subjects are continuously enrolled; therefore, they were followed up for various periods. GEE models are particularly suited to the analysis of data with unequal numbers of measurements per individual and unequal periods between measurements. The analyses were adjusted for organ transplant group, age, gender, education, living alone, depressive symptomatology and the number of months between pretransplant measurement and the transplantation date [24]. The latter variable was included because the intervals between completing the pretransplant PSQ and receiving the transplant could vary substantially. Differences in nonadherence across and within organ groups were compared by adding the interaction terms 'organ' and 'measurement time' to the regression analysis and specifying relevant contrasts. Time was considered a categorical variable (pretransplant, month 6, 12, 24 and 36), except with the sub-analysis testing post-transplant IMNA between organ types (month 6 through month 36).

To test whether pretransplant MNA was predictive for post-transplant IMNA, a similar logistic regression model using GEE was fitted with pretransplant MNA as a covariate.

Three sensitivity analyses were conducted to check the robustness of the findings in relation to the sample included and scoring of the nonadherence variable. A first sensitivity analysis included patients initially excluded from the study due to not taking pretransplant medication. A second sensitivity analysis included only patients with completed adherence assessments until the 2nd year post-transplant. The third sensitivity analysis used ordinal scores of the taking nonadherence variable instead of the dichotomous score (see outcome variable definitions in variables and measurement section).

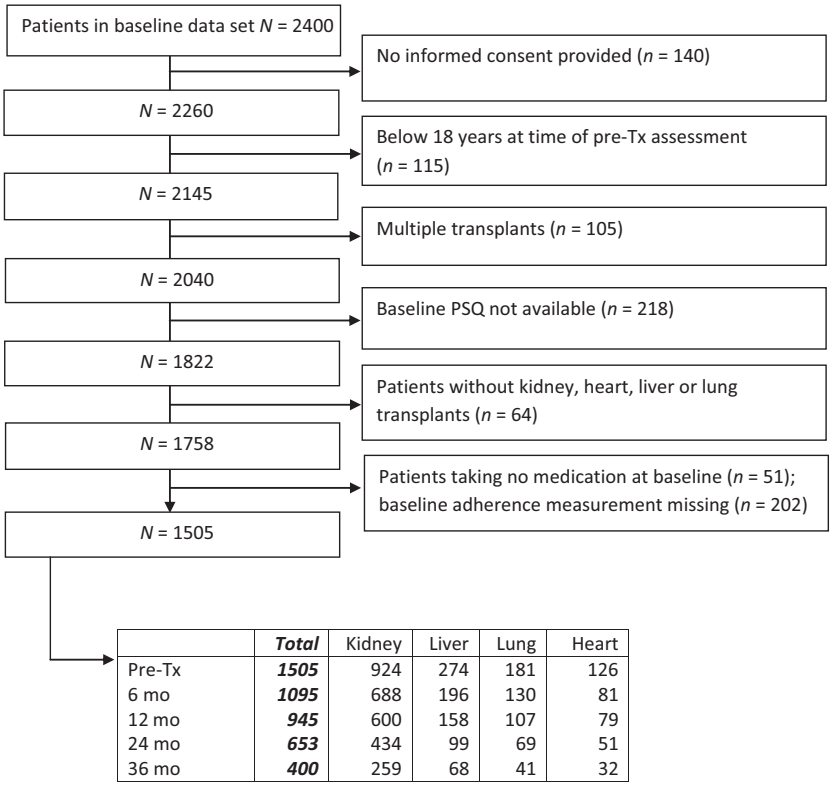
All analyses were performed using SAS 9.3.1. (SAS Institute Inc., Cary, NC, USA). The level of significance was set at $P < 0.05$.

Results

Sample characteristics

As of August 2013, 1505 of 2400 STCS patients fulfilled the inclusion criteria for the current study (see Fig. 1). Because STCS enrolment is continuous and all eligible patients were included in the analysis irrespective of the duration of post-transplant follow-up, various numbers of patients can be observed for the different follow-up times (Fig. 1). Only a limited number of patients dropped out of the study prior to closure due to death ($n = 154$), moving away ($n = 4$), and graft dysfunction ($n = 38$). Figure 1 provides the overall sample size and the figures per individual organ group at each data collection point.

At the time of transplantation, the average age of patients was 52.5 (SD: 13.1) years, almost two-thirds were male (63.7%), and most were married or living with a partner



	Total	Kidney	Liver	Lung	Heart
Pre-Tx	***1505***	924	274	181	126
6 mo	***1095***	688	196	130	81
12 mo	***945***	600	158	107	79
24 mo	***653***	434	99	69	51
36 mo	***400***	259	68	41	32

Figure 1 Flowchart showing the included sample as selected from the STCS overall sample. Tx, transplantation; PSQ, Psychosocial Questionnaire.

(66.6%). Of the four transplant groups, kidney recipients were the largest group (61.4%), followed by liver (18.2%), lung (12.0%) and heart (8.4%) patients (Table 1).

Description of the evolution of MNA

The evolution of MNA is depicted in Fig. 2. Overall MNA decreased from pretransplant to 6 months post-transplant, after which IMNA increased consistently from 6 months to 3 years post-transplant. The overall magnitude of reported taking nonadherence was 26.6% at the time of pretransplant enrolment, 7.6% at 6 months, 12.3% at 1 year, 14.1% at 2 years and 17.4% at 3 years (Table 2; Fig. 2). The magnitude of drug holidays was highest pretransplant (4.1%), and remained relatively stable during the post-transplant observation period (1.4% at 6 months, 1.9% at 1 year, 1.9% at 2 years and 0.9% at 3 years) (Table 2).

Relevant differences in magnitude and evolution of MNA were found among the four organ groups. The variability among organ groups in view of pretransplant MNA was greater compared to post-transplant IMNA; lung and kidney transplant candidates showed the highest MNA pretransplant and heart transplant candidates the lowest, while liver transplant patients reported the highest levels of post-transplant IMNA. Post-transplant IMNA increased in all four organ transplant groups compared to pretransplant magnitude of MNA. The evolution of MNA in lung transplant patients' was comparable to the evolution of the overall sample with the exception of a decrease at 3 years post-transplant (Table 2; Fig. 2).

Comparison of nonadherence within and among solid organ transplant groups

Inferential statistical analysis confirmed that, compared to heart transplant candidates, pretransplant MNA was consistently higher in liver (adjusted odds ratio (aOR): 3.47; 95% CI: 1.70–7.08), kidney (aOR: 5.02; 95% CI: 2.59–9.75) and lung transplant candidates (aOR: 5.11; 95% CI: 2.47–10.53). Liver transplant candidates showed significantly lower levels of MNA pre-transplant compared to kidney (aOR: 0.69; 95% CI: 0.49–0.98) transplant candidates. No significant pretransplant differences were found either between lung and kidney recipients (aOR: 0.98; 95% CI: 0.68–1.41), or between liver and lung recipients (aOR: 1.47; 95% CI: 0.93–2.31).

During the post-transplant period, significantly higher IMNA was found in liver recipients compared to heart (aOR: 2.23; 95% CI: 1.15–4.31) and lung transplant cases (aOR: 2.88; 95% CI: 1.50–5.52). Also, IMNA in kidney

Table 1. Sample characteristics (n = 1505).

Variable	Specification variable	Values
Age at time of Tx	Mean (SD) in years	52.5 (13.1)
Gender	Female – *n* (%)	546 (36.3)
Marital status, *n* (%)	Single	266 (17.7)
	Married/living together	1002 (66.6)
	Widow/widower	40 (2.6)
	Divorced	149 (9.9)
	Separated	36 (2.4)
	Answer refused	12 (0.8)
Highest completed educational degree, *n* (%)	No completed school or professional education	66 (4.4)
	Mandatory school (9 years)	341 (22.7)
	Vocational school	598 (39.7)
	Qualified for university	80 (5.3)
	Higher professional education	130 (8.6)
	Higher school	84 (5.6)
	University, college	143 (9.5)
Organ type, *n* (%)	Kidney	924 (61.4)
	Liver	274 (18.2)
	Lung	181 (12.0)
	Heart	126 (8.4)
Depressive symptomatology – HADS total score	Mean (SD)	8.7 (1.8)
Time between inclusion in STCS and Tx	Median (interquartile range) in months	8.4 (0.2–12.7)

Tx, transplantation; STCS, Swiss Transplant Cohort Study; HADS, Hospital Anxiety and Depression Scale [15].

transplant patients was higher than that of lung transplant patients (aOR: 2.00; 95% CI: 1.10–3.65).

The evolution of nonadherence in the entire sample (Fig. 2; Table 3) showed that the odds of MNA pre-transplant were over four times higher at enrolment than 6 months post-transplant (aOR: 4.61; 95% CI: 3.58–5.94). However after the 6-month assessment, odds of post-TX IMNA were almost three times higher by month 36 (aOR: 2.75; 95% CI: 1.97–3.85). Within each organ group, a pattern of increasing post-transplant IMNA was observed (kidney aOR: 1.02; 95% CI: 1.01–1.04; liver aOR: 1.03; 95% CI: 1.01–1.06; lung aOR: 1.03; 95% CI: 0.99–1.06; heart aOR: 1.05; 95% CI: 1.01–1.08). A *post-hoc* test showed that the decrease in IMNA among lung transplant patients between months 24 and 36 was not significant (P = 0.15). This deviation from the overall pattern might result from the small sample size (N = 46) at 36 months post-transplant.

Pre-transplant MNA as a risk factor for post-transplant IMNA

Pre-transplant MNA predicted post-transplant IMNA with an adjusted odds ratio of 3.04 (95% CI: 2.28–4.04) in univariate analysis. Multivariate analysis confirmed this finding (aOR 3.10; 95% CI: 2.29–4.21) (Table 3).

Sensitivity analysis

A first sensitivity analysis focused on patients who were not prescribed medications pretransplant (N = 51). The preva-

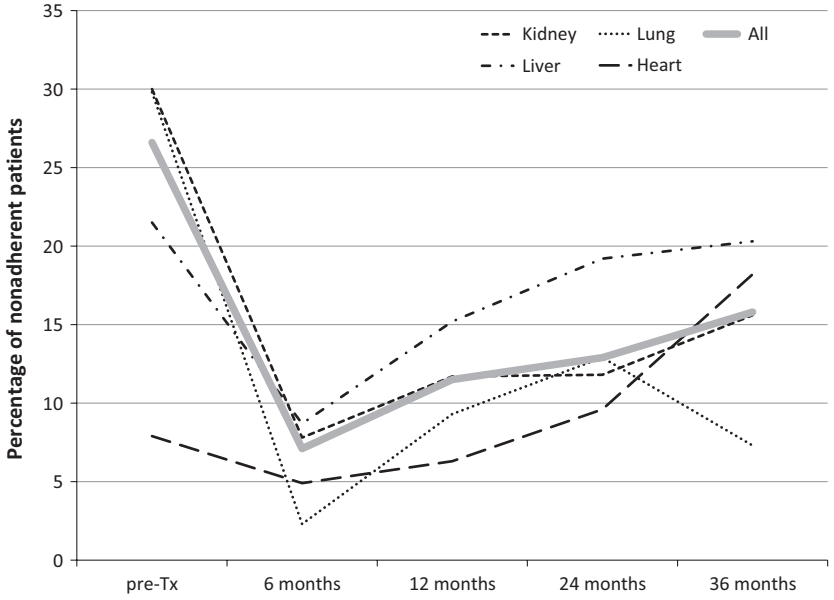


Figure 2 Evolution of medication nonadherence from pretransplant to 3 years post-transplant. Tx, transplantation.

Table 2. Magnitude of nonadherence (taking nonadherence and drug holidays) at different observation points overall, among and between organ groups.

	All organs		Per solid organ transplant group		
Assessment time	Taking nonadherence: *N* (%)	Drug holidays: *N* (%)	Organ	Taking nonadherence: *N* (%)	Drug holidays: *N* (%)
Pre-Tx	400 (26.6)	53 (4.1)	Kidney	277 (29.0)	41 (5.1)
			Liver	59 (21.5)	8 (3.4)
			Lung	54 (29.8)	2 (1.4)
			Heart	10 (7.9)	2 (1.9)
6 months	79 (7.6)	11 (1.4)	Kidney	55 (8.5)	8 (1.6)
			Liver	17 (9.4)	3 (2.2)
			Lung	3 (2.3)	0 (0)
			Heart	4 (5.1)	0 (0)
12 months	110 (12.3)	13 (1.9)	Kidney	71 (12.5)	8 (1.8)
			Liver	24 (16.2)	3 (2.6)
			Lung	10 (9.6)	1 (1.3)
			Heart	5 (6.5)	1 (1.9)
24 months	86 (14.1)	8 (1.9)	Kidney	52 (12.8)	5 (1.8)
			Liver	20 (22.7)	1 (1.3)
			Lung	9 (13.0)	1 (2.3)
			Heart	5 (10.6)	1 (3.1)
36 months	65 (17.4)	2 (0.9)	Kidney	41 (17.3)	1 (0.7)
			Liver	15 (23.8)	0 (0)
			Lung	3 (7.3)	0 (0)
			Heart	6 (18.8)	1 (7.1)

Tx, transplantation. The table presents the valid percentages.

Table 3. Modelling of nonadherence over time and across different organ transplants.

		Evolution of medication nonadherence from pre- to 3 years post Tx (n = 1475)		Prediction of post-Tx nonadherence by pre-Tx nonadherence (n = 1166)§	
Parameter	Contrast	Adjusted odds ratio (95% Confidence limit)	*P*	Adjusted odds ratio (95% Confidence limit)	*P*
Pre-Tx nonadherence		(Variable not included)		3.10 (2.29–4.21)	<0.0001
Data collection point	Pre-Tx versus month 6*	4.61 (3.58–5.94)	<0.0001	(Time point not included)	
	Month 12 versus month 6	1.69 (1.27–2.25)	0.0003	1.69 (1.27–2.25)	0.0003
	Month 24 versus month 6	2.13 (1.58–2.87)	<0.0001	1.15 (1.59–2.92)	<0.0001
	Month 36 versus month 6	2.75 (1.97–3.85)	<0.0001	2.89 (2.05–4.08)	<0.0001
Organ group	Heart versus kidney	0.34 (0.21–0.56)	<0.0001	0.93 (0.49–1.73)	0.81
	Liver versus kidney	1.00 (0.75–1.33)	0.95	1.58 (1.09–2.30)	0.01
	Lung versus kidney	0.76 (0.56–1.05)	0.10	0.49 (0.26–0.90)	0.02
Depressive symptoms		0.96 (0.91–1.01)	0.14	0.96 (0.88–1.04)	0.53
Highest educational degree		1.10 (1.03–1.16)	0.001	1.08 (1.00–1.18)	0.04
Living alone		1.14 (0.91–1.42)	0.22	1.39 (1.01–1.91)	0.04
Age per 10 years		0.77 (0.71–0.85)	<0.0001	0.88 (0.75–1.04)	0.15
Gender	Female versus male	0.82 (0.65–1.02)	0.08	0.92 (0.67–1.26)	0.61
Months between inclusion in STCS and Tx		1.00 (0.99–1.01)	0.61	0.99 (0.98–1.01)	0.74

Tx, transplantation; STCS, Swiss Transplant Cohort Study.
Results of the multivariable logistic regression analysis modelling the odds of (post-transplant) immunosuppressive medication nonadherence. For example the odds ratio in *can be interpreted as the odds of nonadherence at enrolment compared to the reference category of nonadherence 6 months after adjusting for organ, age, gender and time between inclusion in STCS and Tx. The table presents the analysis without interaction term between time and organ.
§This sample (n = 1166) includes all recipients with at least one post-transplant follow-up assessment.

lence of IMNA in this group was 13.5% at 6 months, 5.9% at 12 months, 7.4% at 24 months and 23.1% at 36 months, compared to 7.6%, 12.3%, 14.1% and 17.4% in patients who had been prescribed medications pretransplant ($N = 1505$), respectively. We also observed an increase in IMNA among the pretransplant unmedicated group from 6 to 36 months post-transplant, but the long-term pattern is not as clear as that in the main analysis.

Two other sensitivity analyses, including only patients with completed adherence assessments until the 2nd year post-transplant and using ordinal scores of the nonadherence variable instead of the dichotomous score, respectively, confirmed the robustness of our analyses (see Table 3).

Discussion

The current study used data from patients participating in the STCS, which includes 93% of all patients who have received solid organ transplants in Switzerland since May 2008 [13]. To our knowledge the STCS is the only prospective cohort study in solid organ transplantation that has included medical nonadherence, a major risk factor for poor outcome [2], in its standard assessments [13,14]. The STCS instrument is therefore uniquely useful to study the evolution of MNA from pre-transplant to life-long post-transplant and to assess pretransplant MNA as a risk factor for post-transplant IMNA in all four solid organ transplant groups concurrently.

For the first time, this study used a single methodology to show the concurrent evolution of MNA from pretransplant to 3 years post-transplant in all four major solid organ transplant groups. MNA was highest pretransplant. Across organ groups, less variability was observed in post-transplant IMNA compared to pretransplant MNA (Fig. 2). Despite a decline in magnitude of nonadherence from pre-transplant to 6 months post-transplant, we observed an overall increase in medication nonadherence from 6 to 36 months post-transplant. Other studies have also found IMNA increases over time post-transplant; yet these studies were limited to the first and/or second year post-transplant and only included kidney or cardiothoracic transplant recipients [1,9,10,12,25,26]. Post-transplant, liver transplant patients consistently showed the highest magnitude of IMNA. Further, our analyses demonstrated that pre-transplant MNA was predictive of post-transplant IMNA over 3 years post-transplant. These findings are discussed below in greater detail.

Pretransplant nonadherence

Our description of MNA's magnitude and evolution shows several interesting findings. Pretransplant MNA varied considerably among organ groups, with lung, kidney and liver transplant candidates showing significantly higher levels than heart transplant candidates. This confirms previous findings by our group [27,28]. Heart transplant candidates had the lowest MNA levels pretransplant. This might reflect the extensive pretransplant self-management support offered by Swiss heart failure clinics. The high levels of pre-transplant MNA in the other three solid organ transplant groups warrant attention. In patients with end-stage organ disease, MNA increases the risk of poor clinical outcomes. A meta-analysis by Simpson *et al.* [29] demonstrated that good medication adherence in chronically ill patients is associated with a 24% lower risk for mortality. Given this finding, it might be hypothesized that tackling the issue of MNA pretransplant would reduce waiting list mortality.

Post-transplant nonadherence literature

In view of post-transplant IMNA magnitude among different solid organ transplant groups, our findings compare interestingly with those of previous studies, most of which used cross-sectional designs and included two or more solid organ transplant groups concurrently [10,30–36]. It is also useful to compare them with Dew *et al.*'s meta-analysis [1] summarizing the magnitude of medication nonadherence post-transplant in renal, liver and heart transplant patients. In both cases, our findings include both similarities and contrasts.

A study comparing IMNA among heart and lung transplant patients found lower IMNA in lung recipients than heart recipients (13% vs. 21%, $P = 0.035$) by 2 years post-transplant [10]. And Goetzmann *et al.* [30] found that overall medical regimen nonadherence (including immunosuppressives) was lowest in lung transplant recipients (liver > kidney > heart > lung transplant). However, Germani *et al.* [31] reported lower IMNA in kidney recipients (14%) than in liver (26.2%), heart (26.9%) or lung (30.8%) recipients ($P = 0.008$). Still other studies found no significant differences among heart, liver and lung transplant groups [32–34]. Morales *et al.* [35] found no significant difference in IMNA between liver and kidney transplant recipients. In contrast, Dharancy *et al.* [36] (the French PREDICT study) reported that fewer kidney transplant patients indicated immunosuppressive adherence (27%) than liver transplant recipients (60%); and in a meta-analysis of kidney, liver and heart transplant studies, Dew *et al.* [1] reported that kidney recipients showed the highest IMNA and liver recipients the lowest.

Our finding that liver transplant recipients consistently showed the highest magnitude of IMNA post-transplant is novel, but is in line with another Swiss study [30] reporting that liver transplant patients had the highest level of overall nonadherence compared to lung, heart and renal

transplant recipients. Yet, this finding contrasts with other studies cited above [31–36], as well as with Dew *et al.*'s meta-analysis, in which liver transplant recipients had the lowest nonadherence level. Part of this disagreement may result from Dew *et al.*'s use of studies with disparate designs, sampling methods, measurement methods and operational definitions. Indeed, given that the present study used a single data source (STCS data), and used a single methodology to examine the four organ transplant groups simultaneously, it can be argued that our findings are methodologically very sound and provide the transplant community the most reliable information to date on the magnitude and evolution of MNA within and among the four major solid organ transplant groups.

Pretransplant MNA predicts post-transplant IMNA

Our study also confirmed the findings of Dobbels *et al.* [8] that pretransplant MNA is predictive of post-transplant IMNA. Based on this finding, even before transplantation, patients especially prone to post-transplant IMNA could benefit from preventive and restorative interventions.

Initiation of adherence interventions

Both pretransplant and post-transplant, targeted adherence interventions are best integrated as part of standard care, monitoring IMNA alongside other relevant clinical parameters. Of the medication nonadherence measurement methods currently available, self-reporting is the most accessible, least expensive and simplest to integrate into daily clinical practice [23,37]. The two BAASIS® items used in the STCS can easily be integrated in the clinical interview. Transplant clinicians can also benefit from training in communication and behavioural intervention techniques to tackle IMNA. Various techniques for doing so are described elsewhere [37,38].

Methodological considerations

This study is based on written medication adherence self-reports – collected via the BAASIS© instrument – and a stringent operational definition of IMNA. Three arguments support these choices. First, although patients tend to underreport nonadherence [39], in light of available resources and the size of the STCS, self-reporting was the only feasible assessment method. Second, the authors chose the BAASIS© instrument because, in a recent publication, our group ranked it as one of the top 14 instruments evaluated to assess self-reported IMNA [16]. Recent evidence has shown the predictive and concurrent validity of the BAASIS® in a liver and kidney transplant sample [17]. Finally, our stringent definition of nonadherence (i.e., missing one or more doses over the past 4 weeks) reflects the limited forgiveness of IMNA regarding clinical outcomes in transplantation [2]. Indeed, studies assessing the relationship between subclinical IMNA and acute rejection and/or graft loss in kidney and heart transplantation indicate a clinically meaningful threshold of 5% for IMNA. At the population level, this implies that transplant patients taking <95% of their medications are at a significantly increased risk of poor clinical outcomes [5,11,40].

This study's sensitivity analyses indicated stable patterns of variability among organ groups, the evolutionary pattern, and the findings regarding the predictive value of pretransplant MNA for post-transplant IMNA. This stability suggests robustness in the tested findings.

Focus of future studies in STCS

Further follow-up of the STCS cohort will allow assessment of whether IMNA continues to increase after 3 years post-transplant. Future STCS work will also focus on risk factors for nonadherence by modelling socio-demographic, behavioural, psychosocial and biomedical factors longitudinally in relation to medication nonadherence. It will also focus on assessing the impact of IMNA on outcomes including not only acute rejection, graft loss and mortality, but newer relevant parameters such as renal function [3].

Finally, the STCS did not include sufficient small bowel, pancreatic islet or composite tissue transplants to include the related patient groups in this analysis. Therefore, a number of questions, particularly concerning comparisons of magnitudes and evolutionary patterns of these groups' MNA, remain open for study.

Conclusion

Using the STCS as a research framework, this study is the first prospective assessment of the evolution of MNA to simultaneously study kidney, liver, heart and lung transplant patients from pretransplant to 3 years post-transplant. Pretransplant nonadherence varied between organ groups, with heart transplant patients reporting the lowest levels. A continuous increase was observed in post-transplant IMNA. Liver transplant recipients had the highest level of IMNA post-transplant. Pretransplant nonadherence predicted post-transplant IMNA. It is therefore advisable to assess MNA during pretransplant evaluation, and to target nonadherent patients for early intervention.

Authorship

SDG, HB, LaB, LuB, TRG and KD: participated in research design. SDG, HB, LaB, LuB, TRG, KD and Psychosocial

Interest Group: members participated in writing the paper. SDG, HB, LaB, LuB, TRG, KD, the Psychosocial Interest Group and Swiss Transplant Cohort Study: participated in performance of the research. SDG, TRG and KD: participated in data analysis.

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Appendix

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