

The first report from the patient outcomes registry for transplant effects on life (PORTEL): differences in side-effects and quality of life by organ type, time since transplant and immunosuppressive regimens

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Abstract: Background: Post-transplant patient quality of life (QOL) is affected by a number of different factors. A nationwide patient registry has been established to evaluate QOL and determine the effects of transplant and immunosuppressive regimens on patient outcomes.

Methods: Patients were contacted directly at national meetings, through transplant centers, and patient support groups and invited to participate in the registry. All transplant patients aged 16 and over were eligible to enroll. Patients completed a 100-item self-administered questionnaire consisting of questions about patient demographics, organ functioning, and other post-transplant outcomes. General QOL was measured by the Short form – 12 (SF-12). The Memphis Survey, an instrument developed and psychometrically validated at the University of Tennessee, was administered to patients to evaluate side-effects associated with immunosuppression. Data were analyzed from the first 722 patients who entered the registry. Side-effect profile and QOL outcomes were evaluated by organ type, time since transplant and immunosuppressive regimen. Multiple regression analyses were conducted to determine predictors of post-transplant QOL.

Results: When outcomes were analyzed by organ type, there were no differences in SF-12 or total weighted Memphis scores. Analysis by time since transplant demonstrated that side-effects in the mobility domain increased with patient age and time since transplant. Analysis by immunosuppressive regimen focused on cyclosporine and tacrolimus-based regimens congruent with similar classifications reported in previous studies (PIRSCH JD et al. Transplantation 1997; 63: 977, SHIELD CF III et al. Transplantation 1997; 64: 1738). When analyzed by regimen, there were no differences between the groups in terms of patients reporting good to excellent organ function, treatment for rejection, infection, and over-immunosuppression. Statistically significant differences were observed when side-effect profile was analyzed by immunosuppressive regimen. Patients on cyclosporine-based regimens reported greater overall side-effect severity and more problems with mobility and life roles. Cyclosporine patients also reported more problems in the miscellaneous subscale, including high blood pressure, enlarged gums and hair growth, but less trouble with trembling hands. Multiple stepwise regression models identified several side-effect subscales as having profound effects on mental and physical QOL.

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Conclusion: Transplant recipients report good to excellent levels of QOL, however, side-effects associated with immunosuppressive regimens impair post-transplant QOL. Problems in certain domains, such as mobility, are found to increase with time since transplant. Tacrolimus-based regimens are associated with fewer and less severe side-effects than cyclosporine-based regimens in key domains that affect post-transplant QOL.

Organ transplantation improves patient well-being in many different ways. Previous studies have shown transplantation to benefit health-related quality of life (QOL) and to be cost-effective (1–5).

Although patient and graft survival are remarkably high, opportunities to improve transplant outcomes exist particularly as they relate to patient self-reported indicators of QOL. For example, post-transplant physical QOL still lags behind population norms (5). Dew et al., in a review of QOL studies over a 25-yr span, noted several areas that require further investigation: inter-individual differences in post-transplant QOL (e.g. differences in QOL by organ type), the profile of post-transplant QOL over time, and global vs. domain-specific perceptions of QOL (6). An additional issue that warrants consideration in QOL studies is the observation that individual variability in post-transplant QOL (4, 7–9) confounds our ability to improve outcomes globally and uniformly.

Recent studies have focused on the impact of chronic immunosuppression on post-transplant QOL outcomes caused by the side-effects of the most commonly used immunosuppressive agents (10, 11). Because immunosuppressive therapy is required for the life of the transplant recipient and is accompanied by significant side-effects, and because QOL is increasingly being considered in therapeutic decisions, the relationship between side-effects of immunosuppressive agents and post-transplant QOL is one of the most critical relationships to evaluate in an assessment of post-transplant outcomes.

A nation-wide registry [known as the Patient Outcomes Registry for Transplant Effects on Life (PORTEL)] has been established to evaluate the impact of organ transplantation on patients' lives, determine the effects of immunosuppressive regimens on post-transplant outcomes, and identify predictors of post-transplant QOL. Patients who enroll in the registry are asked to complete a self-administered 100-item instrument consisting of five domains: (1) health factors (organ function, medications and hospitalizations); (2) social factors (socioeconomic status, social support and productivity); (3) major health events (rejection episodes and adverse events); (4) major

life events (family changes and employment); and (5) QOL and related outcomes (physical appearance, general health and disease specific health) (Table 1).

In this first report from the PORTEL, we summarize our findings related to the outcomes (e.g. side-effects, QOL) of transplant patients by organ type, time since transplant, and immunosuppressive regimen. We also assess the determinants of post-transplant QOL of registry participants.

Patients and methods

Patient recruitment and enrollment

Solid organ transplant patients were contacted through various mechanisms including national transplant meetings, referrals from transplant centers, community events, support groups, and direct mail. All transplant patients 16 yr of age or older with functioning grafts were eligible to participate. Patients were invited to participate in the registry without restrictions on the type of transplant received, the amount of time that had elapsed since the date of their transplant, or the type of immunosuppressive regimen that they were on.

Patient confidentiality was assured to all patients, and financial support for the registry (Fujisawa Healthcare, Deerfield, IL, USA) was disclosed to participating providers and patients. Institutional review board (IRB) approval and patient informed

Table 1. Domains captured by the PORTEL registry

Domain	Questions/instruments
Health factors	Organ function Medications Hospitalizations
Social factors	Socioeconomic status Social support Productivity
Major health events	Rejection episodes Adverse events
Major life events	Family changes Employment
QOL and related outcomes	SF-12 (generic) Memphis Survey (disease-specific) Physical appearance (Modified Bergner)

consents were obtained at participating centers when requested and appropriate. No marketing or educational materials were provided to registry participants with survey instruments.

Study design and data collection

The registry was designed as a large observational registry to capture patient-reported outcomes in a real-world environment and to reflect patterns of disease and care. Recruitment occurred through a broad range of settings in order to ensure a diverse study population. Because this is an observational study with ongoing enrollment, no attempt was made to ensure that patients to date who enrolled from a particular center are a random sample of patients seen at that center. Over time, as enrollment in the registry increases, we will be able to stratify patients based on center-specific and national demographics.

Patients were asked to complete a 100-item questionnaire, which took about 20 min to complete. Patients enrolled in the registry were contacted every 6–12 months and asked to complete the questionnaire. The survey instrument was developed by a panel of multidisciplinary transplant clinicians and researchers from across the USA and was organized to collect the following patient variables and outcomes.

Demographics. Patients were asked to report demographics including age, gender, race, socioeconomic status, work status, living arrangements and social support.

Clinical outcomes. Patients were asked to rate transplanted organ functioning (on a scale from ‘0 – not at all’ to ‘5 – perfectly’) and to report comorbidities, hospitalizations and the number of

treatments for rejection, infection and over-immunosuppression.

Medications. Patients reported anti-rejection medications and doses taken in the last 6 months. Patients also reported medications taken for a variety of common comorbidities including diabetes and hypertension.

Side-effects. The frequency and severity of known immunosuppressive side-effects were assessed using a previously developed survey. The Memphis Survey was developed in 1997, independently of the registry, to measure the occurrence (frequency) and impact (severity) of side-effects of immunosuppressive medications on QOL in transplant recipients. It is the only disease-specific instrument developed using a multistage factor analysis designed to capture items of most relevance to transplant recipients on a variety of immunosuppressive medications including cyclosporin, tacrolimus, mycophenolate mofetil and rapamycin. The initial questionnaire included over 100 items representing a wide range of possible problems a patient could face, including headache and hyperglycemia. Following factor analysis, a smaller subset of items emerged as independent factors contributing to QOL. An extensive explanation of the development and validation of the Memphis Survey is provided (Appendix A) (12).

The Memphis Survey has four subscales: emotional burden, life/role responsibilities, mobility, and gastrointestinal distress (GI) distress (Table 2). A fifth subscale includes miscellaneous side-effects (enlarged gums, increased hunger, staying asleep, weight gain, increased hair growth, infections, trembling hands, high blood pressure, easy bruising, loss of interest in sex and sexual performance)

Table 2. Domains of the Memphis Survey

Emotional burden	Life/role responsibilities	GI distress	Mobility	Miscellaneous
Mood changes	Completing daily errands	Stomach pain	Decreased muscle strength	Enlarged gums
Depression	Participating in social activities	Nausea	Climbing stairs	Increased hunger
Nervousness or anxiety	Doing housework	Diarrhea	Walking	Staying asleep
Irritability	Doing yard work	Vomiting	Bone pain	Weight gain
Anger	Performing my job	Stomach gas	Stiff joints	Increased hair growth
Keeping a positive attitude	Participating in physical activities	Indigestion	Foot pain	Infections
Feelings of uselessness	Participating in leisure pastimes		Hip pain	Trembling hands
Being worried	Driving			High blood pressure
Worthlessness	Being independent			Easy bruising
Hopelessness	Ability to travel on vacations			Loss of interest in sex
Ability to concentrate	Reading			Sexual performance

found to be more prevalent during the first 2 yr post-transplant, and were supported by clinician concerns. Symptom experience consists of two different dimensions – symptom occurrence (do you have this problem?) and symptom distress (how troubling is it?) (13). Frequency and severity of each side-effect were coded on a scale of 0–4 from ‘no problem’ to ‘always’ a problem. Participants obtained subscale scores ranging from 0 to 40, with higher scores representing a worse side-effect profile.

Quality of life. Recent reviews in QOL research have demonstrated the importance of including multiple measures of QOL, including both disease-specific and generic instruments as part of a complete health assessment (14, 15). According to a report from the Transplant Outcomes and Research Group titled, *Standards for economic and quality of life studies in transplantation*, a thorough evaluation of health status involves pairing a generic questionnaire with a disease-specific questionnaire (16). In keeping with these recommendations, the Memphis Survey was used to provide a disease-specific perspective and the Short form – 12 (SF-12), a generic QOL instrument, was used to assess overall QOL (17, 18). The SF-12 (QualityMetric, Boston, MA, USA) was designed to be a shorter alternative to the SF-36, the gold standard tool in QOL assessment (19, 20). While the summary measures of the SF-36 comprise an 8-scale health profile, the SF-12 primarily tests patient assessment of physical and mental health, using two summary measures: the Mental Component Summary (MCS) and the Physical Component Summary (PCS). Preliminary tests of reliability and validity have found the SF-12 to be highly correlated with the SF-36 making it an appropriate choice for research studies with large sample sizes and constraints on questionnaire length.

Physical appearance. Due to the known cosmetic side-effects of some immunosuppressive medications, questions about physical appearance were designed based on a previously unpublished Physical Appearance Scale developed by Bergner. This scale has been used in prior studies comparing immunosuppressive agents (21). The questions were developed prior to the initiation of the registry, and were designed to address the effects of immunosuppressive agents on aspects of physical appearance such as satisfaction with appearance and embarrassment as a result of increased hair growth or enlarged gums.

Statistical analyses

Descriptive statistics were generated for patient demographics, clinical outcomes, side-effects, and QOL. In addition, data were analyzed by organ type, time since most recent transplant, and immunosuppressive regimen. Assessments of patient outcomes, side-effects, and QOL were conducted across various immunosuppressive agents, although the analyses focused on cyclosporine- and tacrolimus-based regimens for two reasons. First, several other studies have used a similar classification system to evaluate outcomes (21, 22). Secondly, they represented mutually exclusive groups and were well balanced in terms of the use of other concomitant immunosuppressive agents.

To examine outcomes over time, patients were assigned to clinically relevant discrete groups based on number of years since most recent transplant: <1, 1–2, 3–5, 6–10, and >11 yr. Analysis of variance (ANOVA) and Student’s *t*-tests were performed to test for significant differences between mean values. Chi-square tests were performed to test for differences between categorical variables. P-values of <0.05 were considered statistically significant.

Multiple stepwise regression models were developed to determine the most significant demographic and clinical predictors of QOL (SF-12, MCS and PCS scores). All immunosuppressive medications including azathioprine, cyclosporin, mycophenylate mofetil, predisone, tacrolimus, and sirolimus were entered independently into the regression models. Given the large number of variables collected, techniques were used to screen variables for inclusion. Independent variables with bivariate Pearson’s correlations >0.30 and statistically significant at an alpha of <0.05 were retained (23). All data analyses were performed using SPSS version 10.0.7 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Patient and transplant demographics

From January 2000 to July 2001, 722 transplant recipients enrolled in the registry and provided evaluative data. The mean age was 49.7 (± 13.71) yr and recipients enrolled an average of 4.5 (± 5.13) yr after their most recent transplant. Most patients were Caucasian (81.7%), evenly split between male and female recipients, and most individuals were not working (52.0%). All solid organ transplants were represented except intestinal transplants (Table 3). Most first-time transplant

Table 3. Patient demographics (n = 722)

	Mean (SD)	n ^a (%)
Age	49.73 (13.71)	
Time since most recent transplant	4.5 yr (5.13)	
Race		
African-American		52 (7.2)
Asian American		8 (1.2)
Caucasian		590 (81.7)
Hispanic		35 (4.8)
Other		17 (2.4)
Blank		20 (2.8)
Gender		
Female		336 (46.5)
Male		377 (52.2)
Blank		9 (1.2)
Current work status		
Full or part time		274 (38.0)
Receiving disability		243 (33.7)
Not physically able to work		92 (12.7)
Health insurance		
Medicare/Medicaid		387 (53.6)
Private insurance		450 (62.3)
Both		183 (25.3)
Other		37 (5.1)
Blank		38 (5.3)
Transplant type		
Single transplant		
Heart		141 (19.5)
Kidney		296 (41.0)
Liver		141 (19.5)
Lung		38 (5.3)
Pancreas		6 (0.8)
Intestine		0 (0)
Total repeat transplants		68 (9.4)
All other transplants		32 (4.4)
Immunosuppressive medications		
Azathioprine/Imuran		152 (21.1)
Cyclosporine/Neoral/SangCya		394 (54.6)
FK506/Tacrolimus/Prograf/		290 (40.2)
MMF/CellCept		312 (43.2)
Prednisone		551 (76.3)
Sirolimus/Rapamycin/Rapamune		29 (4.0)

^aNot all subjects responded to all questions, resulting in sample variations across variables.

patients were kidney recipients (41%). The registry included a number of repeat transplant patients, including 32 kidney, 12 liver, and 18 multiple organ recipients (Table 3).

Demographics of the study sample were compared with national data obtained from the United Network for Organ Sharing (UNOS) for comparison. Patients in the registry were similar to the national transplant population in terms of age, gender, and distribution of transplant types. However, African American patients were under-represented in the registry (7.3% in the registry

compared with 17.2% nationwide). Statistical sampling of registry patients was not performed in an attempt to generalize findings to transplant patients nationwide.

Patients reported use of various immunosuppressive agents including prednisone (76.3%), cyclosporine (54.6%), mycophenylate mofetil (43.2%) tacrolimus (40.2%), azathioprine (21.1%) and sirolimus (4.0%). Changes in immunosuppressive regimens could not be evaluated. Not surprisingly, the predominant mutually exclusive groups were patients on cyclosporine- and tacrolimus-based regimens with prednisone, mycophenylate mofetil, and azathioprine evenly distributed across these two groups (Table 4).

Therefore, for purposes of comparing patient/graft outcomes, side-effects, and QOL patients were grouped by primary calcineurin inhibitor regimen: cyclosporine (n = 385) and tacrolimus (n = 283). The group of patients on tacrolimus-based regimens had a significantly lower mean age, a lower mean time since most recent transplant and more females than the group of patients on cyclosporine-based regimens, which may reflect protocols and treatment patterns in the transplant community (Table 5). However, the use of prednisone was evenly distributed between the two groups (Table 4).

Patient outcomes

The majority of patients rated their organ function as being 'good' to 'excellent' (90.4%). High blood pressure was the most commonly reported comorbidity (63.2% of patients). Overall, 8.7% of patients reported being treated for rejection, 17.3% for infection, and 10.9% for over-immunosuppression at some time during the previous 6 months. In addition, 11.2% of patients reported

Table 4. Immunosuppressive regimens of registry patients

Cyclosporine-based regimen	n (%)	Tacrolimus-based regimen	n (%)
C	26 (6.8)	T	53 (18.8)
CA	24 (6.3)	TA	5 (1.8)
CM	29 (7.6)	TM	15 (5.3)
CP	84 (22.1)	TP	66 (23.4)
CPA	77 (20.3)	TPA	27 (9.6)
CPM	126 (33.2)	TPM	108 (38.3)
CPR	5 (1.3)	TPR	5 (1.8)
CPRM	2 (0.5)	TPRM	3 (1.1)
CPAM	4 (1.0)		
CPAR	1 (0.2)		
CR	2 (0.5)		

C = cyclosporine; T = tacrolimus; P = prednisone; A = azathioprine; M = mycophenylate mofetil; R = sirolimus/rapamycin.

	All (n = 722) (%)	Cyclosporine (n = 385) (%)	Tacrolimus (n = 283) (%)	p-Value
Mean age (yr)	49.73	51.66	47.34	<0.001
Time since transplant (yr)	4.5	5.7	2.6	<0.001
<i>Gender</i>				
Female	336 (46.5)	159 (41.3)	147 (51.9)	
Male	377 (52.2)	223 (57.9)	131 (46.3)	<0.01
Blank	9 (1.2)	3 (0.8)	5 (1.8)	
<i>Clinical outcomes</i>				
Rejections (one or more episodes)	63 (8.7)	27 (7.0)	31 (11.0)	NS
Infections (one or more episodes)	125 (17.3)	72 (18.7)	48 (17.0)	NS
Immunosuppression (one or more episodes)	79 (10.9)	42 (10.9)	36 (12.7)	NS
<i>Organ function</i>				
Good to excellent	562 (90.4)	310 (90.1)	212 (91.4)	NS
<i>Hospital admissions</i>				
Hospitalizations (one or more admissions)	81 (11.2)	30 (7.8)	45 (15.9)	<0.01
<i>Comorbidities</i>				
Diabetes	139 (19.3)	77 (20.0)	52 (18.4)	NS
High blood pressure	456 (63.2)	281 (73.0)	143 (50.5)	<0.001
High cholesterol	241 (33.4)	157 (40.8)	63 (22.3)	<0.001
Osteoporosis	160 (22.2)	96 (24.9)	53 (18.7)	NS

Table 5. Clinical outcomes for all patients and by regimen

being hospitalized within the past 6 months for problems related to their transplant (Table 5). There was no difference in the number of hospitalizations by organ type. However, there was a significant difference in the number of hospitalizations by regimen, with patients on tacrolimus reporting more hospitalizations (7.8% vs. 15.9%, $p < 0.01$). Notably, patients with more recent transplants reported a greater number of hospitalizations in the previous 6 months than patients with earlier transplants. As described above, patients on tacrolimus-based regimens had a significantly lower mean time since most recent transplant than patients on cyclosporine-based regimens.

When grouped by immunosuppressive regimen, there were no differences between the groups in terms of patients reporting good to excellent organ function, treatment for rejection, infection, and over-immunosuppression. There were differences in the reported rate of comorbidities between the two groups with patients on a cyclosporine-based regimen reporting a significantly greater likelihood of being treated for high cholesterol (40.8% vs. 22.3%, $p < 0.001$) and high blood pressure (73% vs. 50.5%, $p < 0.001$) in the last 6 months compared with patients on a tacrolimus-based regimen (Table 5).

Side-effects/memphis scores

Symptom frequency was greater than symptom severity in all side-effect domains except the mis-

cellaneous domain, where severity scores were higher (Tables 6 and 7). Overall, patients reported the greatest symptom frequency and severity in the mobility domain of the Memphis Survey.

Analysis by organ type. In terms of organ type, there were no differences in Memphis subscale or total weighted Memphis frequency and severity scores (composite scores based on all the domains of the Memphis Survey). Patients with heart and kidney transplants reported the greatest symptom frequency in the miscellaneous subscale (15.0 vs. 14.7), while patients with liver transplants reported the greatest number of problems with mobility (3, 13).

Analysis by time since transplant. Age and time since transplant affected certain side-effect domains more than others (Table 8). Patients who had more time elapse since their transplants (and thus were treated with immunosuppressives for longer periods of time) reported more frequent and more severe side-effects related to mobility. Mobility frequency and severity scores continued to show an upward trend even when patient scores were adjusted by age. In contrast, scores for the GI and emotional subscales showed no significant increases with time since transplant. Frequency and severity of problems in the miscellaneous domain peaked at 3–5 yr and then declined. Although not statistically significant, patients reported an increase in the severity of problems with life/role responsibilities in the first

Table 6. Memphis Survey scores for all patients and by regimen

	All patients		Cyclosporine		Tacrolimus		p-Value
	Mean	n (SD)	Mean	n (SD)	n (SD)	Mean	
Memphis frequency							
Emotional	11.09	641 (7.32)	11.48	350 (7.68)	10.68	251 (6.76)	NS
Life/role	11.49	639 (10.44)	11.43	347 (10.23)	11.53	249 (10.40)	NS
Mobility	13.82	665 (10.09)	14.65	365 (10.42)	12.88	258 (9.52)	<0.05
GI	8.37	665 (7.16)	8.27	363 (7.32)	8.74	258 (7.08)	NS
Miscellaneous	10.07	651 (7.22)	15.37	359 (7.59)	12.55	250 (6.46)	<0.001
Total weighted	57.60	577 (31.34)	59.64	317 (33.17)	55.66	224 (28.51)	NS
Memphis severity							
Emotional	9.16	629 (8.13)	9.77	345 (8.62)	8.61	246 (7.45)	NS
Life/role	8.57	620 (8.96)	9.29	336 (9.25)	7.81	242 (8.18)	<0.05
Mobility	12.82	643 (10.80)	13.99	353 (11.27)	11.46	250 (10.00)	<0.01
GI	7.34	649 (7.52)	7.33	355 (7.74)	7.66	252 (7.45)	NS
Miscellaneous	12.10	638 (8.04)	13.33	349 (8.34)	10.76	247 (7.52)	<0.001
Total weighted	49.38	539 (33.97)	52.72	295 (35.97)	46.29	212 (30.83)	<0.05

Table 7. Memphis miscellaneous item scores for all patients and by regimen

	All patients		Cyclo		Tacro		p-value
	Mean	n (SD)	Mean	n (SD)	n (SD)	Mean	
<i>Miscellaneous</i>							
Frequency							
High blood pressure	1.74	683 (1.48)	1.93	371 (1.44)	1.49	264 (1.49)	<0.001
Easy bruising	1.87	684 (1.51)	1.97	376 (1.51)	1.76	263 (1.50)	NS
Loss of interest in sex	1.36	675 (1.42)	1.41	369 (1.42)	1.27	261 (1.40)	NS
Sexual performance	1.38	677 (1.38)	1.47	371 (1.38)	1.27	262 (1.38)	NS
Enlarged gums	0.59	678 (1.09)	0.88	371 (1.29)	0.25	263 (0.65)	<0.001
Increased hunger	1.53	678 (1.35)	1.57	367 (1.38)	1.49	268 (1.36)	NS
Staying asleep	1.58	679 (1.36)	1.68	370 (1.37)	1.53	266 (1.34)	NS
Weight gain	1.69	677 (1.40)	1.85	369 (1.38)	1.57	263 (1.42)	<0.05
Increased hair growth	1.52	674 (1.50)	2.08	369 (1.52)	0.77	261 (1.15)	<0.001
Infections	0.81	673 (0.98)	0.90	369 (1.04)	0.68	261 (0.86)	<0.01
Trembling hands	1.58	686 (1.39)	1.36	373 (1.31)	1.95	268 (1.42)	<0.001
Severity							
High blood pressure	1.16	668 (1.25)	1.35	362 (1.27)	0.93	260 (1.17)	<0.001
Easy bruising	1.31	673 (1.39)	1.39	369 (1.39)	1.22	259 (1.40)	NS
Loss of interest in sex	1.27	664 (1.47)	1.38	362 (1.50)	1.12	258 (1.42)	<0.05
Sexual performance	1.37	666 (1.45)	1.53	364 (1.46)	1.18	259 (1.44)	<0.01
Enlarged gums	0.54	675 (1.02)	0.76	369 (1.16)	0.27	263 (0.75)	<0.001
Increased hunger	1.30	668 (1.38)	1.38	359 (1.37)	1.24	266 (1.41)	NS
Staying asleep	1.49	665 (1.40)	1.56	360 (1.40)	1.43	262 (1.38)	NS
Weight gain	1.70	665 (1.53)	1.83	361 (1.49)	1.59	260 (1.58)	NS
Increased hair growth	1.02	661 (1.34)	1.36	359 (1.43)	0.61	258 (1.07)	<0.001
Infections	0.90	663 (1.19)	1.01	363 (1.24)	0.75	257 (1.10)	<0.01
Trembling hands	1.34	672 (1.37)	1.18	364 (1.29)	1.63	263 (1.45)	<0.001

3–5 yr, followed by a decreasing trend until >11 yr.

Analysis by immunosuppressive regimen. There were significant differences in the total weighted Memphis severity score by regimen, with tacrolimus being associated with lower overall symptom severity (46.3 vs. 52.7, $p < 0.05$) than cyclosporine. There were also differences in domain-specific subscale scores by regimen with patients on

tacrolimus-based regimens reporting significantly lower symptom frequency in the mobility (12.9 vs. 14.7, $p < 0.05$) and miscellaneous (12.6 vs. 15.4, $p < 0.001$) domains, and significantly lower symptom severity in the mobility (11.5 vs. 14.0, $p < 0.01$), miscellaneous (10.8 vs. 13.3, $p < 0.001$), and life/role (7.8 vs. 9.3, $p < 0.05$) domains (Table 6).

When individual items of the miscellaneous subscale were examined, patients on tacrolimus-based

Table 8. Memphis Survey scores by time since most recent transplant

	<1 yr		1–2 yr		3–5 yr		6–10 yr		≥11 yr		p-Value
	Mean	n (SD)	Mean	n (SD)	Mean	n (SD)	Mean	n (SD)	Mean	n (SD)	
Memphis frequency											
Emotional	10.72	147 (6.44)	10.89	160 (6.90)	11.11	132 (8.21)	10.76	125 (7.53)	11.87	56 (7.57)	NS
Life/role	12.12	143 (10.39)	10.79	165 (10.48)	12.08	129 (10.99)	11.94	126 (10.37)	9.39	55 (9.65)	NS
Mobility	10.53	149 (7.56)	13.42	169 (10.01)	14.57	139 (10.94)	16.26	130 (10.12)	15.12	58 (11.28)	<0.001
GI	7.61	149 (6.23)	8.89	168 (7.30)	7.34	138 (7.35)	8.72	129 (7.36)	8.97	58 (7.22)	NS
Miscellaneous	13.20	145 (5.85)	13.04	164 (7.09)	15.45	135 (8.13)	14.58	127 (7.45)	14.08	60 (7.62)	<0.05
Memphis severity											
Emotional	8.62	144 (7.24)	8.86	158 (7.40)	9.18	128 (9.12)	9.22	124 (8.62)	9.22	55 (7.93)	NS
Life/role	8.04	138 (7.62)	8.57	163 (9.02)	9.38	123 (10.20)	8.45	123 (8.77)	7.53	54 (9.30)	NS
Mobility	8.99	144 (7.43)	12.51	162 (11.16)	13.37	136 (11.45)	15.65	128 (11.08)	14.70	55 (11.93)	<0.001
GI	6.75	147 (6.65)	7.51	163 (7.63)	6.27	136 (7.07)	7.95	127 (8.00)	8.03	55 (8.46)	NS
Miscellaneous	10.90	142 (6.69)	11.45	159 (8.02)	13.25	133 (8.54)	12.82	126 (8.50)	11.44	58 (8.54)	NS

Variable	Bivariate correlation	p-value	β-coefficient	R ² change	Significance F change*
Emotional severity	-0.731	<0.001	-0.488	0.535	p < 0.001
Living single	-0.167	<0.01	-0.128	0.028	p < 0.001
Income <\$10 000	-0.238	<0.001	-0.095	0.011	p < 0.01
Emotional frequency	-0.713	<0.001	-0.225	0.010	p < 0.01
Care of more people	0.181	0.001	0.119	0.008	p = 0.01
Current age	0.181	0.001	0.104	0.010	p < 0.05

Table 9. Predictors of the SF-12 Mental Component Summary (MCS)

Model R² = 0.601.

*Threshold confidence level for inclusion in the model is p of 0.05.

regimens reported significantly fewer problems than patients on cyclosporine-based regimens with high blood pressure (1.5 vs. 1.9, p < 0.001), enlarged gums (0.3 vs. 0.9, p < 0.001), staying asleep (1.5 vs. 1.7, p < 0.05), hair growth (0.8 vs. 2.1, p < 0.001), and infections (0.7 vs. 0.9, p < 0.01), but significantly more problems with trembling hands (2.0 vs. 1.4, p < 0.001). Trends were similar for side-effect severity (Table 7).

Because of the association of long-term steroid use with bone changes, the impact of prednisone on mobility scores was examined. The presence of prednisone was associated with worse mobility scores. However, tacrolimus patients reported less frequent and severe problems with mobility compared with cyclosporine patients either with or without the presence of prednisone.

Quality of life/SF-12 scores

SF-12 scores for our sample were similar to population norms for the MCS (50.2 vs. 50.1), but were lower for the PCS (42.6 vs. 50.1). The SF-12 scores did not vary by type of organ transplant, immunosuppressive regimen, or by time since most recent transplant.

The results of the stepwise regression models indicated that the strongest predictors of the MCS score were the frequency and severity of problems with emotional burden, living status, income, social support and age. Recipients with higher (better) mental QOL scores reported fewer and less severe problems with emotional burden, were not living alone, had an income of greater than \$10 000, had more than adequate social support and were older than the average patients in the sample. Overall, these variables explained approximately 60% of the variability in the MCS scores (Table 9).

The predictors of the PCS score were problems with mobility, life/role responsibilities, emotional burden, work status and the total weighted frequency score of the Memphis Survey. Patients with higher (better) physical QOL scores reported less trouble with mobility and life/role responsibilities, were able to work full or part-time and had a more favorable overall side-effect profile. Surprisingly, patients with greater emotional burden reported better PCS scores. However, independently, emotional burden did not have a strong correlation with the dependent variable, PCS. Overall, these variables (mobility severity, life/role responsibilities

Table 10. Predictors of the SF-12 Physical Component Summary (PCS)

Variable	Bivariate correlation	p-Value	β -coefficient	R^2 change	Significance F change*
Mobility severity	-0.705	<0.001	-0.452	0.497	$p < 0.001$
Life/role severity	-0.633	<0.001	-0.347	0.077	$p < 0.001$
Emotional severity	-0.359	<0.001	0.271	0.024	$p < 0.001$
Work status (full-time or part-time)	0.336	<0.001	0.136	0.018	$p < 0.001$
Total weighted frequency	-0.654	<0.001	-0.192	0.007	$p < 0.05$

Model $R^2 = 0.623$.

*Threshold confidence level for inclusion in the model is p of 0.05.

severity, emotional burden severity, work status full/part-time and total weighted frequency) explained approximately 62% of the variability in the PCS scores (Table 10).

Discussion

The objectives of this study were to examine differences in side-effects and QOL among patients with different organ types and over time, and the role that immunosuppressive agents have on these post-transplant outcomes. In addition, we attempt to identify factors that are predictive of post-transplant QOL outcomes.

Our findings provide insights into specific aspects of post-transplant QOL as well as general principles of QOL assessment in transplantation. This study establishes a relationship between patient-reported symptom experience, which is sensitive to immunosuppressive regimen, and overall QOL. Notably, scores from the SF-12, a generic QOL measure, did not vary by immunosuppressive regimen or time since transplant. In contrast, the Memphis Survey, a disease-specific measure, revealed numerous differences in patients over time and by immunosuppressive regimen. As reported elsewhere, generic QOL measures may not be sensitive enough to capture differences among various subgroups of post-transplant patients (19). Registry data support the recommendation that it is important to couple disease-specific instruments that have greater sensitivity with generic QOL instruments in order to capture a more accurate picture of QOL outcomes.

Furthermore, the Memphis Survey allows patients to report side-effects along two different dimensions – frequency and severity. Previous research in transplant recipients has shown that the most frequent side-effects of immunosuppressive drugs are not necessarily the most distressing ones and vice versa (13). Our findings support the proposition that the occurrence or frequency of a symptom is different from how distressing it is to the patient. This highlights the importance of including a range of instruments in the assessment

of QOL of transplant patients and that symptom-based assessments should take a multidimensional perspective.

Overall, patients enrolled in the registry have a comparable QOL with transplant recipients assessed in other reports. Specifically, renal transplant recipients enrolled in the registry have a PCS score of 42 and an MCS score of 49, compared with renal transplant recipients evaluated by Pinson et al. with PCS and MCS scores of 40 and 50, respectively (5). Our results also support previously published findings that transplant recipients experience comparable mental QOL compared with the normal population, but experience impaired physical QOL (5).

Analysis of Memphis scores by organ type did not reveal significant differences in side-effect profile. Previous studies using the Memphis Survey in a sample of patients with various organ types have also found that side-effect profiles are similar among recipients regardless of type of organ transplanted (12). Analysis of Memphis subscale scores by time since transplant revealed that side-effect domains varied with post-transplant time. The increase in miscellaneous subscale scores in the first 3–5 yr post-transplant provides evidence that the miscellaneous subscale captures side-effects commonly thought to occur in the first few years following transplant. A finding that deserves further investigation is the curvilinear relationship of life/role responsibilities to time since transplant. The life/role domain inquires about problems such as completing daily errands, doing housework, performing a job or participating in social activities. The increase in life/role severity scores over the first 5 yr, followed by a decrease, might reflect an increasing adaptation among transplant patients to activities of daily living over time.

The choice of immunosuppressive regimen clearly affects patients' appraisals of symptom frequency and impact. Tacrolimus-based regimens were associated with lower overall symptom severity based on a composite of all domains. Tacrolimus-based regimens were also associated with less symptom occurrence and severity in the

key areas that patients reported as most problematic, such as the mobility, life/role and miscellaneous domains.

A number of differences between tacrolimus-based and cyclosporine-based regimens were observed in the analyses of individual items of the miscellaneous subscale, highlighting the importance of regimen choice in minimizing side-effects that are among the most troubling (in terms of severity) to patients. Indeed, items in the miscellaneous domain were reported to impact the lives of patients to a greater extent than side-effects in other domains such as GI and emotional. Because the miscellaneous domain was constructed to reflect symptoms more commonly reported in the first 2 yr following transplant, it was surprising to find that patients on tacrolimus-based regimens scored better on the miscellaneous subscale despite having more recent transplants.

While the differences in mobility scores for the tacrolimus group can be explained by the fact that their mean time since transplant is shorter and they therefore have less exposure to osteopenic-inducing drugs, a similar explanation cannot be offered for the differences found in the life/role and miscellaneous domains. The curvilinear relationship between time since transplant and life/role may be driven by patients on tacrolimus. However, it is unclear whether life/role function for patients on tacrolimus will decline as time passes.

Regression modeling to determine predictors of the SF-12 PCS revealed that patient-reported impact of problems in the mobility, life/role responsibilities and emotional burden domains, in conjunction with work status, were highly predictive of the physical dimension of QOL. These predictors were independent of age and time since transplant. Tacrolimus-based regimens are associated with a more favorable side-effect profile in the domains that contribute most significantly to post-transplant QOL, most notably mobility and life roles. These results confirm previous findings by Hathaway et al. that employment and social support (related to the life/role domain) are highly predictive of post-transplant QOL.

Due to the observational design of this study, certain limitations exist in terms of data analysis and interpretation. Many of these factors have been previously described in similar multi-center, prospective studies (24, 25). One of the limitations of the current study is the extent to which data from registry participants can be extrapolated to the overall transplant population. Although our sample is similar in many aspects to UNOS demographics, we did not force the sample to match the demographic make-up of the national

transplant population. Registry participants were identified through selected channels – for example, outpatient clinics, transplant-related events and patient support groups – and could represent a sample of patients generally more engaged in their own care.

As a consequence of enrolling patients without restrictions on type of immunosuppressive regimen, another limitation is that we could not ensure that the regimen groups were matched in terms of demographic variables. As enrollment in the registry increases, we will be able to conduct additional subset analyses, but in this first report, we emphasize descriptive, cross-sectional data without manipulating the make up of various treatment groups.

In addition, data used for this study were entirely self-reported by transplant recipients and could not be validated by medical records or other sources. Despite these limitations, it is important to underscore the validity, and in fact necessity, of capturing clinical and outcome data from the perspective of the patient. Indeed, health care stakeholders are increasingly recognizing patient self-reported information as a critical factor in the assessment of various treatment options (10, 12). The transplant recipient's appraisal of side-effects is an important perspective in understanding the impact of immunosuppressives on post-transplant QOL and patient decisions regarding therapeutic alternatives and adherence. Health care stakeholders should recognize that patient perception of QOL and the side-effects of long-term therapy are critical considerations in the assessment of therapeutic interventions.

In this report, we presented findings from a large, cross-sectional sample of transplant recipients. As additional patients enroll in the registry, and as longitudinal data become available, we will be able to focus on other trends in clinical, side-effect, and QOL outcomes. Areas of further investigation include changes in side-effect profile and QOL over time, as well as the impact of new immunosuppressive regimens such as steroid and calcineurin inhibitor-sparing protocols on QOL outcomes. The results of these assessments may provide important information to health care decision-makers as they evaluate therapies based on clinical efficacy, cost-effectiveness and patient satisfaction.

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Appendix A: Development and validation of the Memphis Survey

Researchers at the University of Tennessee convened an expert panel of patient care professionals to evaluate side-effects associated with immunosuppressive agents. The expert panel subsequently compiled a 100-item list of common side-effects. An initial survey was piloted with 15 renal transplant recipients who verified content validity and recommended the addition of seven items. The mailed survey included the revised 107-item instrument. Each survey was divided into two parts. Part A asked participants to complete basic demographic data, which included current age, race, gender, time since transplant, level of education achieved, and organ received. A list of medications commonly prescribed was divided into eight categories. Patients were asked to circle each medication that they were currently taking with space provided to write in additional medications. Part B consisted of the list of common side-effects associated with immunosuppressive medications. The first question for each item of Part B asked transplant recipients if they have a particular symptom. Responses to this question were rated on a scale of 0 (never) to 4 (always). The second question for each item asked recipients to rate how troubling they perceived the symptom to be. Responses to this question were also rated on a scale of 0 (not at all) to 4 (extremely).

Once the survey was constructed and piloted, a nationwide survey of transplant recipients (heart, kidney, kidney-pancreas, and liver) was completed. Surveys were mailed to transplant coordinators in 11 centers across the USA and to members of the Transplant Recipient International Organization (TRIO). Centers were recruited through the International Transplant Nursing Society listserv. Transplant coordinators who responded were contacted personally and had the study explained to them. After receiving permission from each

institution, the questionnaires were distributed to transplant recipients as they came through the clinic. Postage and questionnaires were provided for return of the completed questionnaires. The national TRIO office was contacted and surveys were mailed to members, again return postage was provided.

The survey data underwent orthogonal factor analysis to first determine shared relationships between each of the 107 items. As the items clustered or loaded, the variables were grouped by the shared variances among the items. Factors separated as the items lost shared variance. Acceptance for factor loading was set *a priori* at >0.3 . Using this approach, four factors were found to have the best conceptual fit with our purpose. Cronbach α values >0.8 were used to determine item reliability and inclusion in the final instrument. This analysis yielded four subscales, which were labeled emotional burden (EB), life/role involvement (LR), gastrointestinal distress (GI), and mobility (MO). An additional subscale (miscellaneous; MISC) was added using items reported to be most troubling during the early post-transplant course by transplant clinicians. These items did not initially emerge as significant factors in the original analysis, perhaps due to the influence of time on the symptom experience. Because of this, the survey data from patients <2 yr post-transplant were re-analyzed by factor

analysis using the same procedure noted above. Forty-four items were identified as significant, 17 of which were already included in the previous four factors. Of the 27 remaining items, the transplant clinicians were asked to identify 10 items that were clinically important for inclusion in a fifth subscale. The end result of the factor analysis was a 45-item survey with five subscales (EB, LR, GI, MO and MISC). The national data were re-analyzed for differences between organ types, cyclosporine- or tacrolimus-based therapy, presence or absence of prednisone and use of mycophenolate mofetil, and time from transplantation using only the 45 items as determined by the factor analysis.

Subscale scores were tabulated by multiplying the frequency item score by the impact item score, adding these together, and then dividing by the number of items in each subscale. This score was then multiplied by 10, so that weighted subscale scores could then be compared equally with other subscales. Subscale scores ranged from 0 to 40 with lower scores representing less impact of the side-effect on quality of life. The median score of 80 indicates either particular individual items were distressful or that many of the side-effects are perceived at low levels most of the time. A total scale score was calculated by adding each weighted item score (frequency \times impact), dividing the score by 45 and multiplying by 10. Total scale scores range from 0 to 160.