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Factors Associated with Self-Rated Health after Kidney Transplantation: A Prospective Study

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Key Words

Kidney transplantation · Self-rated health · Glomerular filtration rate · Rejection · Immunosuppressant side effects

Abstract

Background: This prospective study explores and compares the relationship between patients' self-rated health (SRH) after kidney transplantation (KT) at different follow-up periods and its medical and nonmedical predictors over time. **Methods:** Patients (n = 128) who completed a questionnaire (the SRH question of the SF-36 and the End-Stage Renal Disease Symptom Checklist – Transplantation Module) were enrolled. Clinical data were retrieved from medical files. The sample was stratified into early (n = 89) and late (n = 39) cohorts according to time since KT at baseline. Linear regression was used to identify predictors of SRH at follow-up. **Results:** In both cohorts, a change in glomerular filtration rate (GFR) over time remained a predictor of SRH; in the early cohort, age was an additional predictor; in the late cohort, a change in transplantation-associated psychological distress over time and the number of late acute rejection episodes

during the observation period were additional predictors. **Conclusions:** Improvement in GFR over time predicted better SRH at each period after KT. Decreased transplantation-associated psychological distress and fewer late acute rejection episodes seemed to predict better SRH at a later follow-up period. Despite these observations, higher SRH was associated with better clinical outcomes.

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Introduction

Self-rated health (SRH) is considered a reliable indicator of mortality and morbidity in patients with end-stage renal disease (ESRD) [1, 2]. Thong et al. [3] investigated the predictive utility of SRH, measured shortly after the start of dialysis, on mortality and found SRH to be an independent predictor of mortality in dialysis patients at up to 7 years of follow-up. Spiegel et al. [4] indicated in their systematic review of ESRD the importance of SRH as it is connected with traditional biomarkers. Avitzur et al. [5] explored SRH in pediatric patients who were 10-year sur-

vivors of transplantation and who had an excellent graft function and a high self-reported quality of life. Thus, SRH seems to be a predictor of future health status and has become an important outcome criterion in the evaluation of medical treatment of ESRD [6].

In previous studies of patients after kidney transplantation (KT), improvements in SRH have been found to be associated with younger age, male gender, higher education, higher socioeconomic status, higher social support and lower number of comorbidities – not only with the success of the transplantation [7]. Studies in ESRD have focused mainly on associations between components of better self-perceived health and objective factors of higher graft function [8, 9]. The subjective evaluation of the side effects of immunosuppressants [10] as well as rejection episodes continues to be a significant problem in long-term attrition of graft function [11], and also seems to be connected to poorer SRH [10].

To our knowledge, there is only one study analyzing the associations between a change in objective factors over time and SRH at follow-up [12]. In addition, studies comparing predictors in SRH in prospective studies stratified by time after KT are lacking. Thus, the aim of this study was (a) to explore changes over time in the medical and nonmedical factors associated with SRH, and (b) to compare their associations with SRH according to time since transplantation.

Materials and Methods

Sample and Procedures

A total of 187 kidney transplant recipients in their 3rd ($n = 134$) and 12th ($n = 53$) month after successful transplant surgery at the Transplant Centre of Kosice from the Eastern Region of Slovakia were invited to participate at baseline examination. The sample was stratified according to time since KT at baseline and 2 cohorts of patients were formed: early patients (3 months after KT at baseline) and late patients (12 months after KT at baseline). The follow-up examination took place in the 12th month after KT for the early cohort and in the 24th month after KT for the late cohort. All patients with a functional transplanted kidney ($n = 142$) who agreed to participate were included. The baseline examination for our sample was performed in the 3rd and 12th month after a successful KT. We did this because the first 3 months after KT are usually considered as the most problematic period which is associated with dramatic changes, increased morbidity and even mortality [13]. Additionally, an improvement in self-perceived health most often occurs during the first 2 years after KT [14]. The exclusion criteria were the presence of mental retardation, organic psycho-syndrome, severe dementia or other psychiatric diseases mentioned in the medical record. Altogether, 3 patients (1.6%) were excluded at the baseline examination, 7 (3.7%) refused to participate, 33 (17.6%) provided incomplete questionnaires and 2

(1.1%) died after baseline; thus, 142 patients (75.9%) were included in the analysis. At follow-up, 14 patients (9.9%) provided incomplete questionnaires, resulting in 128 patients with a functional transplanted kidney (a response rate of 90.1%) at the follow-up examination. Figure 1 presents more detailed information about the participants.

Data collection took place from 2003 to 2010 in Kosice. Patients provided information about sociodemographic variables and filled in the questionnaires. All participants were interviewed during regular outpatient clinical visits by trained personnel independent of the transplant team. Medical data were retrieved from medical records.

Only patients who signed informed consent prior to the study were included. The local ethics committee of Kosice approved the study.

Measures

Sociodemographic data included age and gender. SRH was measured using the first question of the Short-Form Health Survey (SF-36) [15]. The SF-36 questionnaire consists of eight subscales: physical functioning, physical role limitations, bodily pain, vitality, general health perception, social functioning, emotional role limitations and mental health [15, 16]. All of the eight subscales are coded and transformed into a scale from 0 (poor health) to 100 (excellent health) in which they are presented as standard SF-36 scores between 0 and 100, with higher scores indicating better health status [15]. SRH can also be determined in this way from a single item in the SF-36. The validity and reliability of the SF-36 and its first item have been confirmed in patients with renal disease, including those after KT [8, 16–18].

Side effects of immunosuppressive treatment were assessed by the End-Stage Renal Disease Symptom Checklist – Transplantation Module (ESRD SCL-TM), which consists of six subscales: limited physical capacity (10 items), limited cognitive capacity (8 items), cardiac and renal dysfunction (7 items), side effects of corticosteroids (5 items), increased growth of gum and hair (5 items) and transplantation-associated psychological distress (8 items) [19]. This questionnaire can be used to measure the side effects of immunosuppressive treatment as well as its disease-specific distress [19]. For each item, the patient can rate the severity of the symptom on a subscale from 0 (not at all) to 5 (extremely). The scores for the subscales are transformed into a scale score by dividing the severity index score by the number of items in the subscales [19]. Higher scores indicate a higher level of side effects from immunosuppressive treatment. In this sample, Cronbach's α was 0.89 for limited physical capacity, 0.87 for limited cognitive capacity, 0.85 for cardiac and renal dysfunction, 0.81 for side effects of corticosteroids, 0.85 for increased growth of gum and hair and 0.84 for transplantation-associated psychological distress.

Clinical data were retrieved from medical files. These included serum creatinine, weight, duration of dialysis (in years), current immunosuppressive treatment, function immediately after KT, number of early acute rejection episodes, number of late acute rejection episodes and chronic renal allograft dysfunction during the observation period. Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula [20]. Rejection episodes (early acute, late acute and chronic renal allograft dysfunction) were diagnosed after biopsy according to the Banff 2009 update on diagnostic categories for renal allograft biopsies [21]. An early acute rejection episode was defined as an acute rejection

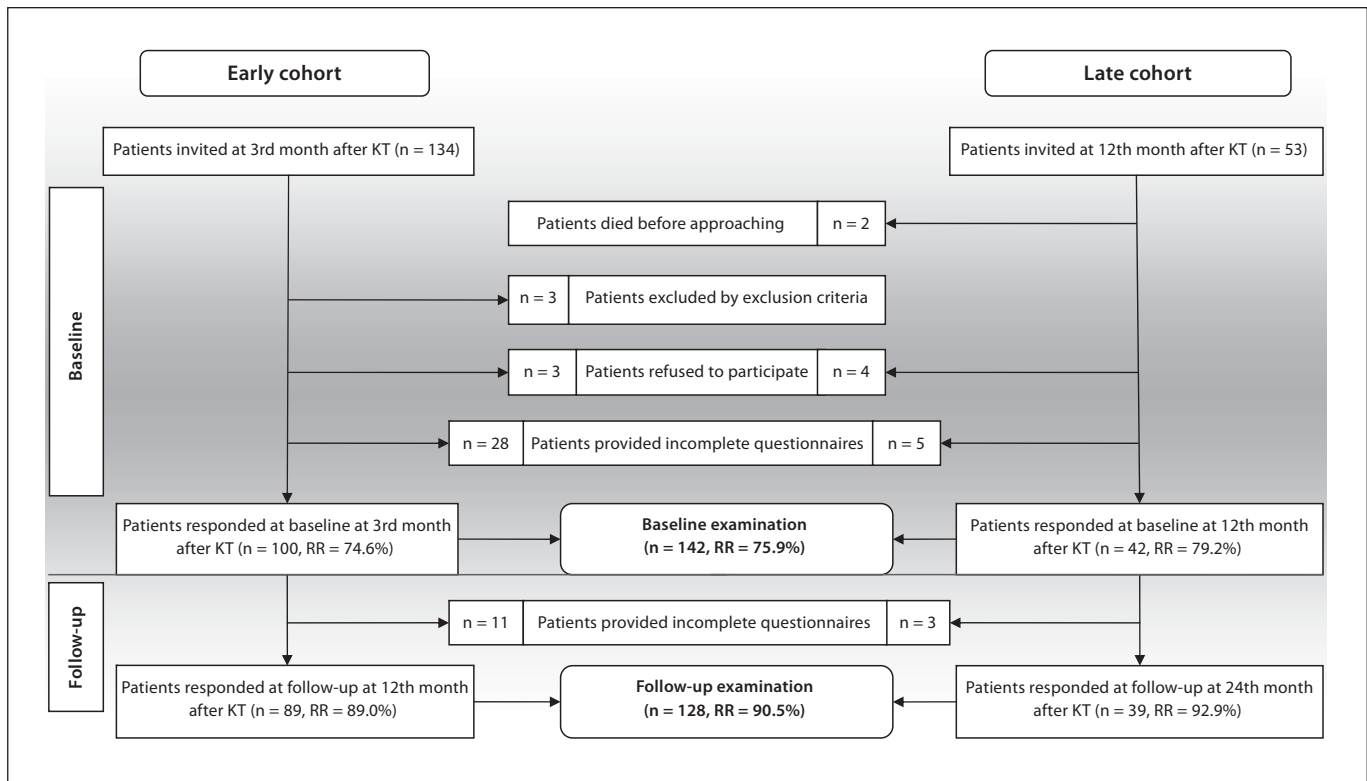


Fig. 1. Flowchart diagram of the participants. RR = Response rate.

episode occurring within 3 months, and a late acute rejection episode was defined as the last acute rejection episode occurring after 3 months independently of a previous early acute rejection episode [22, 23].

Statistics

The Mann-Whitney U test and χ^2 test were used to check the differences between respondents and nonrespondents. Frequencies, means and standard deviations were calculated for the sample description. Bivariate analyses were used for determining the strength and direction of the association between SRH at baseline and follow-up in both cohorts stratified by time after transplantation and the others factors. Stepwise linear regression was performed in order to identify the predictors of SRH at follow-up in the cohorts stratified by time after transplantation (early cohort means 3 months and late cohort means 12 months from baseline). The independent variables were age, gender, change in all six subscales of the ESRD SCL-TM questionnaire over time (between baseline and follow-up examination) and SRH at baseline from the SF-36 questionnaire, the change in GFR over time (between baseline and follow-up examination), duration of dialysis (in years), the number of early acute rejection episodes, the number of late acute rejection episodes, and chronic renal allograft dysfunction during the observation period. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, Ill., USA) version 16.0 was used for statistical analyses.

Results

No significant differences were found between respondents and nonrespondents regarding age, gender and medical factors, or between patients who provided complete and incomplete data. In addition, no significant differences regarding the independent variables were found between the cohorts stratified by time after transplantation at baseline and at follow-up.

In both cohorts, the side effects of immunosuppressive treatment and the mean limited physical capacity significantly increased over time (between baseline and follow-up; $p \leq 0.01$); on the other hand, the mean transplantation-associated psychological distress significantly decreased over time ($p \leq 0.05$). The mean SRH significantly increased over time ($p \leq 0.001$) as did the mean GFR over time ($p \leq 0.001$). Other variables did not significantly differ from baseline to follow-up. The pairwise associations for SRH at baseline and follow-up in the cohorts with each of the factors are indicated in table 1.

Gender, the change in five subscales of the ESRD SCL-TM over time (limited physical capacity, limited cogni-

Table 1. Sociodemographic, psychological and medical characteristics of the sample at baseline and at follow-up

		Baseline (n = 142)	Follow-up (n = 128)
Time after KT during reviewing	3 months	100 (70.5)	0
	12 months	42 (29.5)	89 (69.5)
	24 months	0	39 (29.5)
Age (mean ± SD)		48.7 ± 12.7*	49.7 ± 12.7*
Gender	male	79 (55.6)	70 (54.7)
	female	63 (44.4)*, #	58 (45.3)
ESRD SCL-TM	limited physical capacity	1.51 (0.97)*	1.77 (0.97)*, #
	limited cognitive capacity	1.22 (0.82)*	1.31 (0.86)*
	side effects of corticosteroids	1.09 (0.92)	1.08 (0.78)
	cardiac and renal dysfunction	1.04 (0.81)*	1.07 (0.84)*
	increased gum and hair growth	0.76 (0.92)	0.78 (0.86)
	transplantation-associated psychological distress	1.28 (0.85)*	1.17 (0.81)*, #
SRH (mean ± SD)		47.82 ± 24.55	57.66 ± 24.43
GFR, ml/s (mean ± SD)		0.99 ± 0.28	1.12 ± 0.37*, #
Function immediately after KT	immediate function	74 (52.1)	66 (51.6)
	delayed function	68 (47.9)	62 (48.4)
Immunosuppression treatment at the time of interview	CsA+MMF+P	84 (59.2)	80 (62.5)
	Tac+MMF+P	40 (28.2)	39 (30.5)
	Tac+MMF	3 (2.1)	1 (0.8)
	CsA+MMF	10 (7.0)	8 (6.2)
	SIR+MMF+P/SIR+MMF	5 (3.5)	0
Duration on dialysis, years		3.65 (2.44)	3.51 (2.32)
Number of early acute rejection episodes during observation period		0.32 (0.55)*	0.31 (0.53)*
Number of late acute rejection episodes during observation period		0.15 (0.36)#	0.15 (0.35)#
Chronic renal allograft dysfunction during observation period		0.14 (0.35)	0.13 (0.32)#

Values in parentheses represent percentages. Significant differences between baseline and follow-up are in bold font.

Determining the strength of the association between SRH and each variable: * SRH in the early cohort; # SRH in the late cohort.

tive capacity, cardiac and renal dysfunction, the side effects of corticosteroids, and increased growth of gum and hair), duration of dialysis, the number of early acute rejection episodes during the observation period, and chronic renal allograft dysfunction during the observation period were not predictors associated with SRH at follow-up in the regression models of the stratified cohorts.

The regression model of the early cohort (n = 89) explained 66.2% of SRH variance at follow-up. A change in GFR over time contributed significantly to this model, as did age and SRH at baseline.

The regression model of the late cohort (n = 39) explained 60.4% of SRH variance at follow-up. A change in

GFR over time contributed significantly to this model, as did a change in transplantation-associated psychological distress over time, the number of late acute rejection episodes during the observation period, and SRH at baseline. More detailed information is presented in table 2.

Discussion

In this study we (a) explored changes over time in medical and nonmedical factors associated with SRH, and (b) compared their associations with SRH at follow-up for early and late cohorts stratified by time since transplantation. Over a follow-up observation period in the

Table 2. The regression models of significant predictors of SRH at follow-up in the cohorts: early (model 1) and late (model 2)

Models	Standardized coefficient β	95% CI
<i>Model 1 in the early cohort (n = 89); adjusted R² 0.662</i>		
Constant		19.476; 52.544
SRH at baseline	0.644***	0.484; 0.744
Change in GFR over time	0.569***	48.572; 77.037
Age	-0.160**	-0.553; -0.050
<i>Model 2 in the late cohort (n = 39); adjusted R² 0.604</i>		
Constant		11.363; 42.099
SRH at baseline	0.600***	0.326; 0.859
Change in GFR over time	0.555***	19.110; 57.104
Change in transplantation-associated psychological distress over time	-0.338**	-14.810; -2.360
Number of late acute rejection episodes	-0.306*	-33.698; -2.975
* p < 0.05; ** p < 0.01; *** p < 0.001.		

early and late cohorts, SRH and GFR increased, while transplantation-associated psychological distress decreased. Previous studies have found an association between a higher GFR rate and better SRH [8, 9].

In the early cohort, worse SRH at baseline as well as at follow-up was associated with elderly, higher limited physical capacity, higher limited cognitive capacity, higher cardiac and renal dysfunction, higher transplantation-associated psychological distress and early acute rejection episodes. Additionally, worse SRH at baseline was associated with female gender and, at follow-up, with lower GFR. In the late cohort, worse SRH at baseline, as well as at follow-up, was associated with late acute rejection episodes. Moreover, worse SRH at baseline was associated with female gender and, at follow-up, lower GFR, higher limited physical capacity, higher transplantation-associated psychological distress and chronic renal allograft dysfunction. Associations between elderly, females, individual evaluations in disease-specific distress, rejection episodes and poorer well-being were also found [7–9, 18].

A change in GFR over time consistently predicted SRH at follow-up in both cohorts. Furthermore, better SRH at follow-up was predicted by fewer late acute rejection episodes during the observation period in the late cohort after KT. Age was a predictor of SRH at follow-up in the early cohort only.

Our results indicate important differences in predictors of SRH at follow-up in the early cohort compared to the late cohort after KT. For the early cohort after KT, a

change in GFR over time and age are predictors associated with SRH at follow-up. We have previously reported similar results in a smaller sample [12]. However, in the late cohort after KT, in addition to the change in GFR over time, the change in transplantation-associated psychological distress over time and the number of late acute rejection episodes during the observation period contributed significantly to the explanation of the variance in SRH at follow-up.

Late acute rejection episodes during the observation period seem to have a significant relationship to SRH at a late period after KT. So far, late acute rejection episodes cause lower GFR and poor SRH. Moreover, a decreased GFR predicts poor SRH, and not only when it occurs during late acute rejection episodes. Djamali et al. [24] showed that decreased graft function after late acute rejection is associated with poor patient and allograft survival, which might be connected to poor SRH as well. Individual perceptions in disease-specific distress of transplantation also give the impression of having a significant relationship to SRH at a late period after KT. Similar to our findings, Drent et al. [25] divided their group of transplanted patients into short- and long-term cohorts and showed differences between these groups: the long-term cohort reported more individual negative experiences than the short-term cohort did.

Strengths and Limitations

The strength of this study is its longitudinal design, which enabled us to explore changes in factors associated with SRH as well as the associations between these changes and SRH at follow-up in the early and the late cohorts stratified according to time after KT. Missing data is a limitation of this study; however, there were no differences in age and gender between respondents and nonrespondents. On the other hand, all consecutive patients originating from one major transplant center in Slovakia over a number of years were asked to participate in the study to prevent selection bias.

Recommendations and Implications

Results must be verified in a larger sample to allow for generalization. In addition, we only studied patients from baseline to 3 and 12 months after transplantation; therefore, prolonging the study period is necessary. Thus, in a future study, pretransplantation SRH is needed to further study its role in influencing post-transplantation SRH at follow-up. We could then verify whether SRH after KT remains dependent on the factors found in the cohorts before transplantation, or whether in a longer period af-

ter KT other variables become important. Furthermore, the pathways between psychological, physical and medical determinants associated with SRH should be studied.

In conclusion, improvement in graft function over time predicted better SRH at each period of follow-up. Decreased transplantation-associated psychological distress did not seem to be important in the first year after KT, instead only beyond 1 year after KT. Moreover, fewer late acute rejection episodes seemed to predict better SRH at a late follow-up period. Despite these observations, higher SRH was associated with better clinical outcomes.

References

- 1 Benjamins MR, Hummer RA, Eberstein IW, Nam CB: Self-reported health and adult mortality risk: an analysis of cause-specific mortality. *Soc Sci Med* 2004;59:1297–1306.
- 2 Benyamini Y, Idler EL, Leventhal H, Leventhal EA: Positive affect and function as influences on self-assessments of health: expanding our view beyond illness and disability. *J Gerontol B Psychol Sci Soc Sci* 2000;55:107–116.
- 3 Thong MSY, Kaptein AA, Benyamini Y, Krediet RT, Boeschoten EW, Dekker FW: Association between a self-rated health question and mortality in young and old dialysis patients: a cohort study. *Am J Kidney Dis* 2008;52:111–117.
- 4 Spiegel BMR, Melmed G, Robbins S, Esrailian E: Biomarkers and health-related quality of life in end-stage renal disease: a systematic review. *Clin J Am Soc Nephrol* 2008;3:1759–1768.
- 5 Avitzur Y, De Luca E, Cantos M, Jimenez-Rivera C, Jones N, Fecteau A, Grant D, Lee Ng V: Health status ten years after pediatric liver transplantation – looking beyond the graft. *Transplantation* 2004;78:566–573.
- 6 DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P: Mortality prediction with a single general self-rated health question. A meta-analysis. *J Gen Intern Med* 2006;21:267–275.
- 7 Rebollo P, Ortega F, Baltar JM, Diaz-Corte C, Navascues RA, Naves M, Urena A, Badia X, Alvarez-Ude F, Alvarez-Grande J: Health-related quality of life (HRQOL) in end stage renal disease (ESRD) patients over 65 years. *Geriatr Nephrol Urol* 1998;8:85–94.
- 8 Fujisawa M, Ichikawa Y, Yoshiya K, Isotani S, Higuchi A, Nagano S, Arakawa S, Hamami G, Matsumoto O, Kamidono S: Assessment of health-related quality of life in renal transplant and hemodialysis patients using the SF-36 health survey. *Urology* 2000;56:201–206.
- 9 Saracino A, Gollo I, Di Noia I, Caldane MG, Santarsia G, Procida C, Latorraca A, Gaudiano V: Loss of renal function is associated with deterioration of health-related quality of life in kidney transplant patients. *Transplant Proc* 2008;40:3460–3465.
- 10 Hathaway D, Winsett R, Prendergast M, Subaiya I: 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. *Clin Transplant* 2003;17:183–194.
- 11 Srinivas TR, Meier-Kriesche HU: Minimizing immunosuppression, an alternative approach to reducing side effects: objectives and interim result. *Clin J Am Soc Nephrol* 2008;3:S101–S116.
- 12 Majernikova M, Rosenberger J, Prihodova L, Nagyova I, Roland R, van Dijk JP, Groothoff JW: Self-rated health after kidney transplantation and the change in graft function. *Dial Transplant* 2010;39:440–444.
- 13 Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK: Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725–1730.
- 14 Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, Muirhead N: A study of the quality of life and cost-utility of renal transplantation. *Kidney Int* 1996;50:235–242.
- 15 Ware JE Jr, Sherbourne CD: The MOS 36-item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–483.
- 16 Wight JP, Edwards L, Brazier J, Walters S, Payne JN, Brown CB: The SF36 as an outcome measure of services for end stage renal failure. *Qual Health Care* 1998;7:209–221.
- 17 Gomez-Besteiro MI, Santiago-Perez MI, Alonso-Hernandez A, Valdes-Canedo F, Rebollo-Alvarez P: Validity and reliability of the SF-36 questionnaire in patients on the waiting list for a kidney transplant and transplant patients. *Am J Nephrol* 2004;24:346–351.
- 18 Franke GH, Reimer J, Philipp T, Heemann U: Aspects of quality of life through end-stage renal disease. *Qual Life Res* 2003;12:103–115.
- 19 Franke GH, Reimer J, Kohnle M, Luetkes P, Maehner N, Heemann U: Quality of life in end-stage renal disease patients after successful kidney transplantation: development of the ESRD Symptom Checklist – Transplantation Module. *Nephron* 1999;83:31–39.
- 20 Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
- 21 Sis B, Mengel M, Haas M, Colvin RB, Halloran PF, Racusen LC, Solez K, Baldwin III WM, Bracamonte ER, Broecker V, Cosio F, Demetris AJ, Drachenberg C, Einecke G, Gloor J, Glotz D, Kraus E, Legendre C, Liapis H, Mannon RB, Nankivell BJ, Nickleit V, Papadimitriou JC, Randhawa P, Regele H, Renaudin K, Rodriguez ER, Seron D, Seshan S, Suthanthiran M, Wasowska BA, Zachary A, Zeevi A: Banff '09 Meeting Report: antibody mediated graft deterioration and implementation of Banff working groups. *Am J Transplant* 2010;10:464–471.
- 22 Sijpkens YWJ, Doxiadis IIN, Mallat MJK, de Fijter JW, Bruijn JA, Claas FHJ, Paul LC: Early versus late acute rejection episodes in renal transplantation. *Transplantation* 2003;75:204–208.
- 23 Joseph JT, Kingsmore DB, Junor BJ, Briggs JD, Mun Woo Y, Jaques BC, Hamilton DN, Jardine AG, Jindal RM: The impact of late acute rejection after cadaveric kidney transplantation. *Clin Transplant* 2001;15:221–227.
- 24 Djamali A, Samaniego M, Torrealba J, Pirsch J, Muth BL: Increase in proteinuria >200 mg/g after late rejection is associated with poor graft survival. *Nephrol Dial Transplant* 2010;25:1300–1306.
- 25 Drent G, Moon P, De Geest S, Kleibeuker JH, Haagsma EB: Symptom experience associated with immunosuppressive drugs after liver transplantation in adults: possible relationship with medication non-compliance? *Clin Transplant* 2008;22:700–709.

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Disclosure Statement

The authors have no conflicts of interest.