Title
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Journal
International Urology and Nephrology, 44(3)

ISSN
0924-8455

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Publication Date
2012-06-01

DOI
10.1007/s11255-011-0088-6

Int Urol Nephrol (2012) 44:945–954
DOI 10.1007/s11255-011-0088-6

NEPHROLOGY - ORIGINAL PAPER

Roma ethnicity and clinical outcomes in kidney transplant recipients

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Received: 18 August 2011 / Accepted: 4 November 2011 / Published online: 25 November 2011

Abstract
Background Racial and ethnic disparities among North American patients with chronic kidney disease have received significant attention. In contrast, little is known about health-related outcomes of patients with end-stage renal disease among the Roma minority, also known as gypsies, compared to Caucasian individuals. We prospectively assessed the association between Roma ethnicity and long-term clinical outcomes in kidney transplant recipients.
Methods In a prevalent cohort of renal transplant recipients, followed up over a median of 94 months, we prospectively collected socio-demographic, medical (and transplant related) characteristics and laboratory data at baseline from 60 Roma and 1,003 Caucasian patients (mean age 45 (SD = 11) and 49

Electronic supplementary material The online version of this article (doi:10.1007/s11255-011-0088-6) contains supplementary material, which is available to authorized users.

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(SD = 13) years, 33 and 41% women, 18 and 17% with diabetes mellitus, respectively). Survival analyses examined the associations between Roma ethnicity and all-cause mortality and death-censored graft loss or death with functioning renal allograft.

Results: During the follow-up period, 341 patients (32%) died. Two-hundred eighty (26%) patients died with a functioning graft and 201 patients (19%) returned to dialysis. After multivariable adjustments, Roma ethnicity was associated with 77% higher risk of all-cause mortality (Hazard Ratio (HR): 1.77; 95% confidence interval (CI): 1.02, 3.07), two times higher risk of mortality with functioning graft (2.04 [1.17–3.55]) and 77% higher risk of graft loss (1.77 [1.01–3.13]), respectively.

Conclusions Roma ethnicity is independently associated with increased mortality risk and worse graft outcome in kidney transplant recipients. Further studies should identify the factors contributing to worse outcomes among Roma patients.

Keywords Roma ethnicity · Kidney transplantation · Mortality, graft loss

Introduction

Racial and ethnic disparities exist among individuals who suffer from chronic kidney disease (CKD) in the United States (US) and elsewhere. [1–3] Approximately one-third of the 400,000 US dialysis patients are African American, although they only comprise only 14% of the US general population [4, 5]. Among the US general population without CKD, disparities in income, education, diet, lifestyle, co-morbid conditions and access to healthcare have been implicated in the higher mortality of African Americans compared with Whites [6]. In contrast to the tendencies observed in the general population, African American and Hispanic patients with end-stage renal disease (ESRD) [7] appear to experience consistently better survival than non-Hispanic Whites [4, 5]. These differences and disparities have received much attention in the literature recently.

In contrast, very little is known about health-related outcomes of the Roma in Europe, also referred to as the Gypsy minority. Gypsies or the Roma consider themselves originated from Egypt. They have arrived in Europe from India in the 12th–14th centuries through Turkey and partially Africa stretching across country borders [8, 9]. Currently, there are about 12 million Roma living in Europe mainly in Eastern and Central European countries, but also in Italy, Spain, England, etc. In some countries like Macedonia, Bulgaria, Romania and Slovakia and Hungary, an estimated 7–9% of the population are of Roma origin. [10, 11] Issues concerning the Gypsies, just as any race-related question, are sensitive. During their several hundred years of history in Europe, Gypsies have had different experiences: accepted, tolerated or rejected. During the II World War, it is estimated that 0.5-1 million Gypsies were executed [12]. A significant proportion of the Roma population in Europe still faces significant socio-economic challenges as poverty and unemployment is usually quite high among this population, in part due to insufficient integration and under-education. This large and culturally distinct ethnic group has an estimated population of 12 million individuals and is dispersed across Eastern and Central Europe. Smaller Roma populations exist in most of the Western European countries. In some countries like Macedonia, Bulgaria, Romania, Slovakia and Hungary, it is estimated that about 7–9% of the population belong to the Roma [13]. Sporadic data indicate that risk factors of ESRD such as diabetes, metabolic syndrome, obesity, hypertension and cardiovascular disorders are more prevalent in the Roma population than in Caucasians [14–17]. Moreover, the clinical presentation of systemic lupus erythematosus also appears to be different in Roma compared to Caucasian patients [18]. Thomas et al. reported that the prevalence of CKD is high (20%) in the Roma population [14]. There are limited data about the prevalence and the outcomes of Roma patients with ESRD, that is, individuals undergoing maintenance dialysis or who are kidney transplant recipients. An earlier analysis from the same center reported worse long-term allograft survival in Hungarian Roma patients [19].

Using data obtained from a prevalent cohort of stable kidney transplant recipients, also including individuals with Roma background, we analyzed the association between ethnicity and long-term clinical outcome. We hypothesized that Roma patients experience worse graft and patient survival, even after adjustment for important clinical characteristics.

Subjects and methods

Patient population and data collection

All patients 18 years of age or older ($n = 1{,}191$) who were regularly followed at a single kidney transplant outpatient clinic at the Department of Transplantation and Surgery at Semmelweis University, Budapest were invited to participate in our prospective prevalent cohort study. Of 1,191 patients, 1,067 agreed to participate of the study. Baseline assessments were conducted between August 2002 and February 2003 (Transplantation and Quality of Life-Hungary Study (TransQoL-HU Study)) [20–25]. All patients underwent kidney transplantation between 1977 and 2002. Patients with an acute rejection or infection within 1 month of enrollment, those with transplant vintage less than 3 months, those with dementia and those who refused to participate were excluded.

Demographic data and details of medical history were collected at enrollment including age, gender, marital, educational, employment and financial status, etiology of CKD, the presence or absence of diabetes, hypertension and other co-morbidities were obtained from medical records. Laboratory measurements performed at baseline included blood hemoglobin (Hb) and serum C-reactive protein, creatinine, urea nitrogen and albumin concentrations. Transplant-related data were extracted from the medical records and included the following information: medications (including current immunosuppressive treatment), transplant vintage (time elapsed since transplantation), last available and highest level of panel reactive antibody (PRA), cold ischemia time, number of HLA mismatches, presence of delayed graft function, history of acute rejection, donor gender, age and type; and recipients' blood group. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) study equation [26].

The study was approved by the Ethics Committee of the Semmelweis University (67/2002 and 70/2002). Before enrollment, patients provided written informed consent based on detailed written and verbal information about the aims of the study and its procedures.

Patients were followed for a median of 94 months (interquartile range: 72-95 months). The primary outcome measure was all-cause mortality (including deaths with functioning graft or after return to dialysis therapy). Secondary outcome measures were death-censored graft loss and death with a functioning graft. Death-censored graft loss was defined as return to maintenance dialysis. Deaths and re-initiations of maintenance dialysis were ascertained from the hospital records. Deaths were validated by cross-referencing with data from the Hungarian Central Office of Administrative and Electronic Public Service.

Assessment of ethnicity

Patients were categorized as Roma or non-Roma-Caucasian by two physicians independently who provided direct clinical care for all patients. Any discrepancies in their initial assessment were reassessed and reconciled via consensus to provide a final determination of the "Roma" designation.

Self-reported co-morbidity

Information about the presence or absence of co-morbid conditions was obtained by interviewing the patients, as previously described [27]. A self-reported co-morbidity score was calculated by summing up the number of co-morbid conditions that the patients reported. Our earlier studies indicated that this comorbidity score correlates significantly with mortality and provides valuable information about the overall clinical and health condition of the patients [21, 23, 27–29].

Immunosuppressive therapy

Standard immunosuppressive therapy consisted of an oral steroid (prednisolone), a calcineurin inhibitor, either cyclosporine A (Neoral™) (CsA) or tacrolimus (Prograf™), and a 3rd immunosuppressive agent, that is, mycophenolate mofetil (MMF), azathioprine or rapamycin.

Statistical analysis

Statistical analyses were carried out using the STATA 11.1 (StataCorp LP, Texas) and SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina) software packages. Data were summarized using proportions, means (±standard deviation, SD) or medians (interquartile range, IQR), as appropriate. Categorical variables were analyzed with Chi-square

test, and continuous variables were compared using Student's t test, Mann–Whitney U test, Kruskal–Wallis H test or ANOVA, as appropriate. In all statistical analyses, two-sided tests were employed, and the results were considered statistically significant if the P value was <0.05.

The association between Roma ethnicity and all-cause mortality was assessed using Cox regression analysis. We also assessed the association between Roma ethnicity and all-cause mortality using left truncated Cox regression analysis as sensitivity analysis. As death with functioning graft and graft loss are competing events, the association of Roma ethnicity with these two outcomes was assessed by means of semiparametric competing-risks regression analyses using the method of Fine and Gray [30].

Variables entered in the multivariable models were selected based on theoretical considerations; we included predictors in the models which were known to be associated with mortality based on external evidence and clinical experience, and which were available in our database. For each analysis, three models were examined based on the level of multivariable adjustment:

(I) Unadjusted model that included only the Roma or Caucasian ethnicity;
(II) Age, gender and estimated GFR adjusted models;
(III) All of the above plus serum albumin, serum CRP, hemoglobin, number of co-morbid conditions and total time with end-stage kidney disease.

In sensitivity analyses, we also examined the association between Roma ethnicity and outcomes in different separate multivariate models. The proportionality assumption was tested using Schoenfeld residuals. Variance inflation factors were used to assess collinearity between independent variables.

Results

Socio-demographic and clinical characteristics of the sample

A detailed description of the study sample has been reported in several prior publications [24, 25, 31]. The patients' follow-up process is shown in Fig. 1. Out of 1,067 kidney transplant recipients, four patients were lost to follow-up. The final study population, therefore, included 60 Roma and 1,003 Caucasian patients. The baseline characteristics are shown in Table 1. Crude graft loss rates were higher in Roma patients. Roma patients were younger, had lower education level and were more likely to report financial difficulties and more likely to be re-transplanted patients. Other socio-demographic parameters were similar between Roma and Caucasian patients.

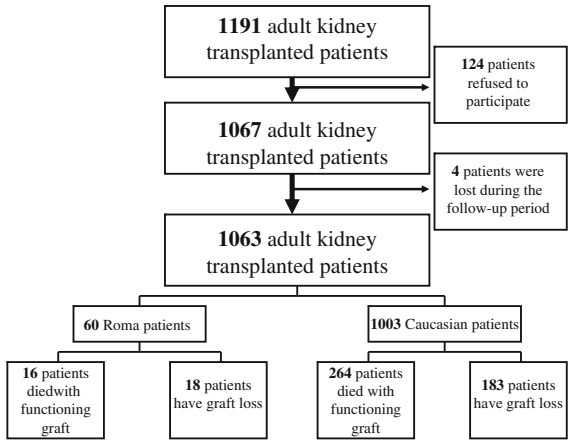

Fig. 1 Flow chart of patients' classification

Outcomes

During the follow-up period (94 months), 341 patients (32%) died including 280 (26%) patients with a functioning graft, while 201 patients (19%) returned to dialysis. The crude mortality rate was 49.7/1,000 patient-years (95% confidence interval (CI): 44.7–55.2). The unadjusted mortality rate was similar among Roma and Caucasian patients (crude mortality rate in Roma patients: 47.9/1,000 patient-years (95% CI: 30.6–75.1) and in Caucasian patients: 49.8/1,000 patient-years (95% CI: 44.6–55.5); $P = 0.87$).

Table 2 shows the outcomes associated with Roma versus Caucasian ethnicity. Roma ethnicity was not associated with all-cause mortality in unadjusted and age, gender and eGFR-adjusted models. After adjustment for other covariates, however, Roma ethnicity was associated with a 77% higher risk of all-cause mortality (Hazard Ratio (HR): 1.77; 95% CI: 1.02, 3.07) (Table 2). Results were similar in left truncated Cox regression analyses (Table 2) and after

Table 1 Patients' characteristics

	Roma patients ($n = 60$)	Caucasian patients ($n = 1003$)	P value*
Male—*n* (%)	40 (67)	592 (59)	0.24
Age (years) (mean ± SD)	45 ± 11	49 ± 13	0.04
Marital status: married *n* (%)	29 (64)	549 (66)	0.82
Self assessed financial situation: *n* (%)			
Financial problems presents	12 (27)	106 (13)	0.02
Have just enough money	16 (35)	289 (35)	
No financial problems	17 (38)	437 (53)	
Employed: *n* (%)	2 (6)	113 (16)	0.09
Level of education (%)			0.001
Primary education or less	18 (40)	144 (17)	
Skilled workers	9 (20)	236 (28)	
High school or equivalent	14 (31)	273 (33)	
University diploma	4 (9)	178 (22)	
BMI (kg/m^2)	25.1 ± 4.8	25.1 ± 4.4	0.95
Diabetes—*n* (%)	8 (18)	138 (17)	0.87
Chronic pulmonary disease *n* (%)	1 (3)	26 (3)	0.80
Chronic cardiac disease *n* (%)	9 (23)	229 (29)	0.41
Peripheral vascular disease *n* (%)	7 (18)	240 (31)	0.10
Chronic mineral bone disease *n* (%)	8 (21)	262 (33)	0.12
Number of co-morbid conditions (median; min–max)	1; 0-6	2; 0-7	0.18
Transplant vintage (months) (median (IQR))	52 (17–75)	56 (26–88)	0.06
Cumulative ESRD time (months) (median (IQR))	68 (36–102)	76 (49–116)	0.11
Serum albumin (g/l) (mean ± SD)	42.0 ± 3.0	41.5 ± 3.4	0.38
Hemoglobin (g/l) (mean ± SD)	134 ± 20	132 ± 19	0.44
Serum C-reactive protein (mg/l) (median (IQR))	2.5 (1–6)	3 (1–7)	0.75
eGFR (ml/min/1.73 m^2) (mean ± SD)	51 ± 17	49 ± 22	0.55
HLA mismatches *n* (%)			0.99
0	2 (4)	29 (3)	
1	6 (10)	107 (11)	
2	17 (30)	269 (28)	
3	19 (34)	372 (38)	
4	10 (18)	156 (16)	
5	2 (4)	40 (4)	
6	0 (0)	3 (0)	
Re-transplanted patients *n* (%)	11 (18)	78 (8)	0.005
Donor age (years) (mean ±SD)	42 ± 13	41 ± 14	0.54
Donor gender (male) *n* (%)	31 (56)	630 (66)	0.14
Donor type (living) *n* (%)	4 (7)	34 (4)	0.17
Delayed graft function *n* (%)	18 (32)	255 (27)	0.36
History of acute rejection *n* (%)	22 (39)	429 (45)	0.43
Cold ischemia time (hours) (median (IQR))	23 (20-25)	22 (19-24)	0.07
Immunosuppressants: *n*(%)			
Steroids	55 (92)	874 (87)	0.31
Cyclosporin A Neoral	45 (75)	699 (70)	0.38

Table 1 continued

	Roma patients ($n = 60$)	Caucasian patients ($n = 1003$)	P value*
Tacrolimus	12 (20)	161 (16)	0.42
Mycophenolate mofetil	43 (72)	629 (63)	0.16
Azathioprine	7 (12)	129 (13)	0.79
Sirolimus	0 (0)	20 (2)	0.27
Last available PRA before transplantation (%) (median (min–max))	0 (0–60)	0 (0–99)	0.46
Highest available PRA before transplantation (%) (median (min–max))	5 (0–85)	5 (0–99)	0.36
Recipient blood group *n* (%)			0.63
0	11 (20)	267 (27)	
A	26 (46)	393 (40)	
B	11 (20)	188 (19)	
AB	8 (14)	128 (13)	
All-cause death *n* (%)	19 (32)	322 (32)	0.98
Graft loss *n* (%)	18 (31)	183 (18)	0.02

eGFR estimated glomerular filtration rate, *BMI* body mass index, *ESRD* end-stage renal disease, *PRA* panel reactive antibodies, *HLA* human leukocyte antigen

* *P* value of test comparing Roma and Caucasian groups

Table 2 Outcomes associated with Roma ethnicity compared to Caucasian ethnicity

	Unadjusted model	Age, gender and eGFR adjusted model	Multivariate adjusted model[e]
All-cause mortality Hazard Ratio (95% CI)[a]	0.96 (0.61, 1.53)	1.27 (0.80, 2.03)	1.77 (1.02, 3.07)
All-cause mortality Hazard Ratio (95% CI)[b]	1.00 (0.63, 1.60)	1.35 (0.85, 2.16)	1.88 (1.08, 3.26)
Subcohort Hazard Ratio of mortality with functioning graft (95% CI)[c]	0.99 (0.60, 1.62)	1.33 (0.80, 2.21)	2.04 (1.17, 3.55)
Subcohort Hazard Ratio of death-censored graft loss (95% CI)[d]	1.77 (1.09, 2.86)	1.74 (1.08, 2.80)	1.77 (1.01, 3.13)

[a] Cox proportional regression analyses

[b] Left truncated Cox proportional regression analyses

[c] Semiparametric competing-risks regression analyses: competing event: graft loss

[d] Semiparametric competing-risks regression analyses: competing event: death with functioning graft

[e] Models adjusted for age, gender, estimated GFR, serum albumin, serum CRP, hemoglobin, number of co-morbid conditions and total time with end-stage kidney failure

adjustment of different co-variables in a set of sensitivity analyses (Table S1).

Multivariate cumulative incidence plots for mortality with functioning graft according to ethnicity are presented in Fig. 2. Roma ethnicity was independently associated with higher risk of death with functioning graft in the fully adjusted model (Sub-Hazard Ratio (SHR): 2.04; 95% CI: 1.17, 3.55) (Table 2). Similar results were found after adjustment of different co-variables in a set of sensitivity analyses (Table S1).

Roma ethnicity was associated with death-censored graft loss (SHR: 1.77; 95% CI: 1.09, 2.86) in the unadjusted model. This association remained significant after multivariable adjustments (SHR in the fully adjusted model: 1.77; 95% CI: 1.01, 3.13) (Table 2). Similar results were found after adjustment for transplant related variables (Table 2). Multivariate

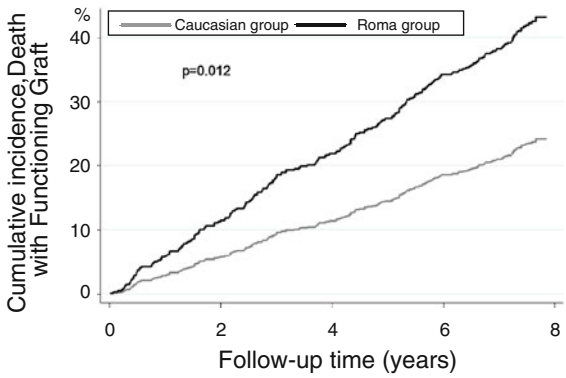

Fig. 2 Multivariable adjusted cumulative incidence curve of mortality with functioning graft in Roma and Caucasian patients. Models were adjusted for age, gender, estimated GFR, serum albumin, serum CRP, hemoglobin, number of co-morbid conditions and total time with end-stage kidney failure

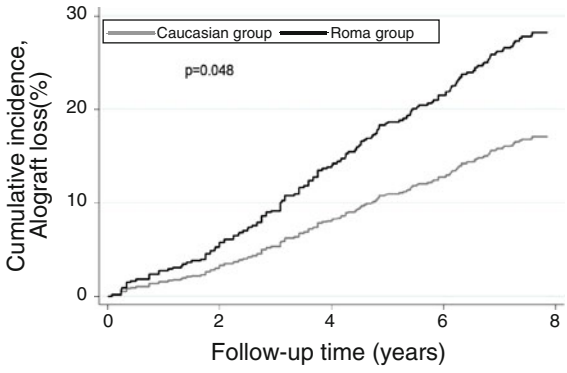

Fig. 3 Multivariable adjusted cumulative incidence curve of allograft loss in Roma and Caucasian patients. Models were adjusted for age, gender, estimated GFR, serum albumin, serum CRP, hemoglobin, number of co-morbid conditions and total time with end-stage kidney failure

cumulative incidence plots for allograft loss according to different ethnicity are presented in Fig. 3. Similar trends were found after adjustment of different co-variables in a set of sensitivity analyses (Table S1).

Discussion

In this 7-year prospective cohort of 1,063 stable, prevalent kidney transplant recipients from a Hungarian center, Roma ethnicity was associated both with all-cause mortality and death with a functioning graft independent of several socio-demographic and clinical co-variables. Moreover, Roma ethnicity was also a significant predictor of death-censored graft loss. These findings may have a major clinical and public health implications, especially for those regions with sizeable Roma populations.

Potential explanations for the observed inferior kidney transplant outcomes among Roma recipients include an increased prevalence of cardiovascular risk factors such as diabetes, metabolic syndrome, smoking, obesity and hypertension [14–17]. Another potential explanation is the impact of socio-economic factors. In our study sample, similarly to the general population, Roma patients were more likely to report financial difficulties, were less educated and more frequently unemployed. Lower socio-economic status is known to be associated with higher prevalence of depression and non-adherence to medical treatment [32], which per se are associated with elevated mortality risk in kidney transplant patients [33, 34]. In a recent study, Voko et al. reported that socioeconomic status is a strong determinant of the health status of people living in Roma settlements in Hungary [35]. Importantly, the association between mortality and Roma ethnicity remained significant after adjusting for socio-demographic variables, but an effect of socio-economic status on the observed outcomes cannot be excluded. Additionally, Roma patients have high prevalence of infectious diseases, in part due to poorer sanitary and living conditions. This further increases their disease burden and potentially impacts on clinical outcomes in this immune-suppressed patient population [36]. Another potential explanation may be the effect of specific genetic background of the Roma, similarly to African Americans, of which very little information is available with regard to health outcomes.

In our 7-years prospective study, Roma ethnicity was associated with 77% higher risk of allograft loss. Similar results were found by Langer et al. [19]. Potential explanation is the different genetic background, which may lead to a greater degree of incompatibility between Roma and Caucasian donor-recipient pairs. Although the HLA mismatches were similar in Roma and Caucasian patients in our sample, the HLA genetics (on split as well as allelic level) may still be different between these groups potentially leading to de novo expression of donor-specific antibodies [37]. Good HLA-A, HLA-B and HLA-DR matches do not guarantee rejection-free renal transplantation. Some kidney transplants fail despite such

close match, indicating that other antigens might be targets for rejection [38]. Major-histocompatibility-complex (MHC) class I-related chain A (MICA) antigens are polymorphic and can elicit antibody production [38]. The probability of a Roma recipient receiving a kidney from a Caucasian donor is higher than a Caucasian recipient receiving a graft from a Roma donor. Consequently, anti-MICA antibodies may be more prevalent in Roma recipients. Presensitization of kidney transplant recipients against MICA antigens is associated with an increased frequency of graft loss and might contribute to allograft loss among recipients who are well matched on HLA loci [38]. Another potential explanation is the different socio-economic status (SES) of Roma patients. As discussed above, Roma patients have a higher risk to experience deprivation which is associated with higher prevalence of depression and non-adherence [32], both factors associated with higher risk of graft loss in kidney transplanted recipients [33, 34]. Additionally, non-adherence and different genetic background might contribute to the higher prevalence of acute allograft rejection in Roma patients.

Furthermore, Roma patients may metabolize immunosuppressive medications differently. The activity of drug metabolizing pathways is influenced by genetic variations similarly to the polymorphism of the CYP2C9 enzyme [39]. Pharmaco-genetic studies need to explore whether Roma transplant recipients have a different allele structure and thus variations in the immunosuppressive regimens or dosing needs to be considered when treating Roma organ recipients.

Our study is notable for the large sample size, prospective design and its long follow-up. Numerous clinical and socio-demographic parameters were collected. To our knowledge, this is the first study that found associations between Roma ethnicity and unfavorable post-transplant outcomes. Several limitations of our study should also be noted when interpreting the results. A limitation of observational studies, such as ours, is that they cannot prove causal associations between predictors and outcomes. Patients from a single center were enrolled; therefore, our results are not to be generalized without further considerations. The proportion of Roma patients was small relative to the non-Roma population. The definition of acute rejection (includes early and late acute rejection) was based on clinical assessment only in about 50% of the cases. Additionally, about half of the patients enrolled in this study had been transplanted prior to 1997, thus did not receive mycophenolate mofetil containing triple therapy and few of them received induction therapy [40, 41]. Information about comorbid conditions was based on self-reports by the patients. However, elements of the ESRD-SI, a valid comorbidity questionnaire [42], were integrated into our tool. In previous analyses, the self-reported comorbidity score correlated significantly with serum albumin and also with mortality in this patient population [29], and we suggest that this score provides valuable information about the overall clinical condition of the renal transplant recipients [27]. Additionally, we do not have data on several other known predictors of mortality and graft loss such as proteinuria, blood pressure, non-adherence, etc., hence residual confounding is possible. Moreover, there is another potential bias to misclassifying patients' ethnic background and the physician bias to label the patients, who are not doing well to Roma ethnicity. Finally, it is possible that patients of Roma ethnicity, who were well, may have migrated to other areas and were being followed up at smaller/regional centers. However, in Hungary, there are only four transplant centers. Our center is the biggest following 60% of all patients. Moreover, the prescription of immunosuppressive drugs is allowed only in these centers, and these centers have to send the report to other centers when the patients have switched center, which is very rare in Hungary.

Conclusions

In a 7-year prospective prevalent cohort from a single large Hungarian kidney transplant center, Roma ethnicity is independently associated with increased death risk and worse graft outcomes in kidney transplant recipients. Ethnicity should be considered when planning medical interventions such as immunosuppression and other therapies in kidney transplant recipients in countries with sizeable Roma minority. Additional studies are needed to assess whether specific, ethnicity-based interventions could improve clinical outcomes in this patient population.

Acknowledgments This study was supported by grants from the National Research Fund (OTKA) (KTIA-OTKA-EU 7KP-

HUMAN-MB08-A-81231), ETT (206/09), the Hungarian Kidney Foundation, Hungarian Society of Hypertension, Hungarian Society of Nephrology and the Foundation for Prevention in Medicine. MZM received grants from the National Developmental Agency (KTIA-OTKA-EU 7KP-HUMAN-MB08-A-81231) from the Research and Technological Innovation Fund, was also supported by Hungarian Kidney Foundation. The research of M. Novak has been supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (2008–2011) and the Center for Integrative Mood Research, Toronto, Canada.

Conflict of interest None.

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