

GENDER DIFFERENCES IN KIDNEY TRANSPLANTATION – 10-YEAR RETROSPECTIVE STUDY

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Abstract

Background: Chronic kidney disease represents a world-wide health problem affecting approximately 195 million women around the world. Risk of development of chronic kidney disease is greater in women; therefore, the World Kidney Day 2018 was dedicated to kidney disease, treatment options, and its specifics in female patients.

Materials and Methods: We retrospectively analysed a cohort of 1,457 patients after kidney transplantation from all transplant centres in Slovakia over a period of ten years from 2005 – 2015. The parameters taken into account were cause of end-stage renal disease (ESRD), outcome of transplantation in a context of differences between the genders.

Results: During the ten-year period there were 557 transplanted women vs. 900 men. Among female recipient the dominant cause of ESRD was tubulointerstitial nephritis (males 22.3% vs. females 32.1%, $p < 0.0001$), other causes of ESRD where females were significantly more represented than men included polycystic kidney disease (males 11.6% vs. females 17.6%, $p = 0.0013$) and systemic lupus erythematosus (males 0.2% vs. females 2.3 %, $p = 0.0001$). There was no significant difference in 12-month, 5-year, and 10-year both graft and patient survival rates between men and women. Female recipients wait for kidney transplantation significantly longer in spite of comparable time spent on dialysis (males 32.9 months vs. females 39.4 months, $p < 0.0001$).

Conclusion: Despite comparable patient and graft survival rates in male and female recipients in our study there are other studies showing that gender as well as gender mismatch significantly influence the outcomes of transplantation.

Key words: kidney transplantation, transplantation outcomes, gender differences

BACKGROUND

Chronic kidney disease is more prevalent in women than men (1); thus, the International Society of Nephrology in joint initiative with the International Federation of Kidney Foundations decided the World Kidney Day 2018 to be dedicated to awareness of impact of kidney disease on women's health. Kidney transplantation represents the best treatment and cost-effective modality of end-stage renal disease.

Therefore, the objectives of our study were to characterise the cohort from the perspective of potential gender differences regarding a cause leading to end-stage renal disease and renal transplantation outcomes.

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METHODS

Our retrospective multi-centric study included 1,457 patients who received a kidney transplant from a deceased donor from 2005 to 2015. The characteristics of our cohort include age at the time of kidney transplantation, degree of transplantation, waiting time, time spent on dialysis, cause of end-stage renal disease, and patient and graft survivals. We used a certified statistical program MedCalc version 13.1.2. (MedCalc Software's VAT registration number is BE 0809 344 640, Member of International Association of Statistical Computing, Ostend, Belgium). Comparisons of continuous variables between the groups were carried out using parametric (t-test) or nonparametric (Mann-Whitney) tests; associations between categorical variables were analyzed using the χ^2 test and Fisher's exact test, as appropriate; Kaplan-Meier analysis was used for survival rates. We consider the value $P < 0.05$ to be statistically significant.

Ethical approval: All procedures involving human participants have been approved according to the ethical standards of the institutional and/or national research committee, including the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

RESULTS

Out of 1,457 patients, 557 (517 primary transplantation) were women, 900 (831) men. Primary causes leading to end-stage renal disease (ESRD) in female recipients where we

Table 1: Characteristics of recipients

	men (n = 900)	women (n = 557)	P value
Age at the time of RTx (years)	46.8 ± 12.3	46.3 ± 13.1	0.4622
Primary Rtx – number (%)	831 (92.3)	517 (92.8)	0.7250
Cause of ESRD:			
TIN (%)	22.3	32.1	<0.0001
GN (%)	38	25.7	<0.0001
DM1 (%)	4	4.8	0.4649
DM2 (%)	7.8	4.1	0.0050
ADPKD (%)	11.6	17.6	0.0013
reflux nephropathy (%)	4.3	4.7	0.7192
IgA nephropathy (%)	2.9	1.1	0.0232
FSGS (%)	4.1	3.1	0.3270
SLE (%)	0.2	2.3	0.0001
Other (%)	4.8	4.5	0.7924

TIN – tubulointerstitial nephropathy; GN – glomerulonephritis; DM1, 2 – type 1 diabetes mellitus 1; type 2 diabetes mellitus; ADPKD – polycystic kidney disease; FSGS – focal segmental glomerulosclerosis; SLE – systemic lupus erythematosus

observed a statistically significant difference between genders were tubulointerstitial nephritis (32.1% in females vs. 22.3% in males, $p < 0.0001$), autosomal dominant polycystic kidney disease (17.6% vs. 11.6%, $p = 0.0013$), and systemic lupus erythematosus (2.3% vs. 0.2%, $p = 0.0001$). In male recipients native kidneys were more frequently affected by glomerulonephritis (38% vs. 25.7%, $p < 0.0001$), nephropathy as a complication of type 2 diabetes mellitus (7.8% vs. 4.1%, $p < 0.0001$), and IgA nephropathy (2.9% vs. 1.1%, $p = 0.0232$). There were no statistically significant gender differences in other causes of ESRD (Tab. 1).

However, there was no significant difference in time spent on dialysis between female and male recipients (39.4 ± 39 months vs. 35.8 ± 33.2 months, $p > 0.05$), female recipients waited for a kidney transplant significantly longer (32.9 ± 27.4 months vs. 39.4 ± 31.5 months, $p < 0.0001$).

Overall death-censored graft survival rates in our cohort in female and male recipients were after 12 months 91.2% vs. 93.1%, $p = \text{NS}$, 5 years 80.7% vs. 82.6%, $p = \text{NS}$, and 10 years 60% vs. 66.7%, $p = \text{NS}$ (Fig. 1).

After 12 months, 5 and 10 years, the overall patient survival rates among female vs. male recipients were 96.8% vs. 97.1%, $p = \text{NS}$; 89.9% vs. 88.9%, $p = \text{NS}$; and 72.9% vs. 76%, $p = \text{NS}$ (Fig. 2), respectively.

DISCUSSION

Our data showed that over the 10-year period only 38% of kidney recipients were female. Although number of studies describing gender representation was very limited, in comparison with other reports, we found 2:3 ratio in favour of men as well (2,3). Regarding the patient and graft survivals, in our cohort we found no statistically significant difference between the genders, yet the female recipients had generally poorer both graft and patient survival. Nevertheless, other studies report that gender does influence the outcomes of transplantation. We cannot assume that there are no other gender differences than within the reproductive system and/or that those could be explained solely by the effect of sex hormones (4,5).

Few discussed mechanisms leading to such disparities include gender differences in immune responses, size, and gender mismatch.

Gender dimorphism of immune system and how sex hormones affect immune responses have been studied for a while now, yet warrants further elucidation (6–8). Factors on the recipients' side encompass the effect of hormones, e.g. the immunosuppressive effect of testosterone (9,10), as well as the potent effects of estrogen and the role of estrogen receptors (11,12). Innate immune pathways are modulated by the activity of estrogen receptors; estradiol most often promotes the production of type I interferon leading to pro-inflammatory cytokine production (13), hence influencing alloimmune response and graft survival (14). Dimorphism is also present in kidney itself, where immunogenicity of male graft is lower than those of female donor and male graft are less susceptible to cold ischemia (15,16).

Puoti et al. in 2016 published a paper where they report the male-donor-to-female-recipient mismatch presented a significant decrease in heart, lung, liver, and kidney graft survival, while the male recipients benefited when they received an organ from a female donor, in particular for heart transplantation (17). The female recipients of male kidney grafts had the poorest outcomes after transplantation and this donor-recipient combination was identified as independent risk factor for inferior graft survival, this negative effect was mitigated when the donor's BMI (Body Mass Index) was 2 units larger (18–20).

Even though non-HLA (Human Leukocyte Antigen) mismatches might not be currently in the centre of attention, minor histocompatibility antigens, such as H-Y, affect the outcomes of transplantation and Y-linked antigens might explain poorer outcomes in female recipients of male grafts (18,21–23).

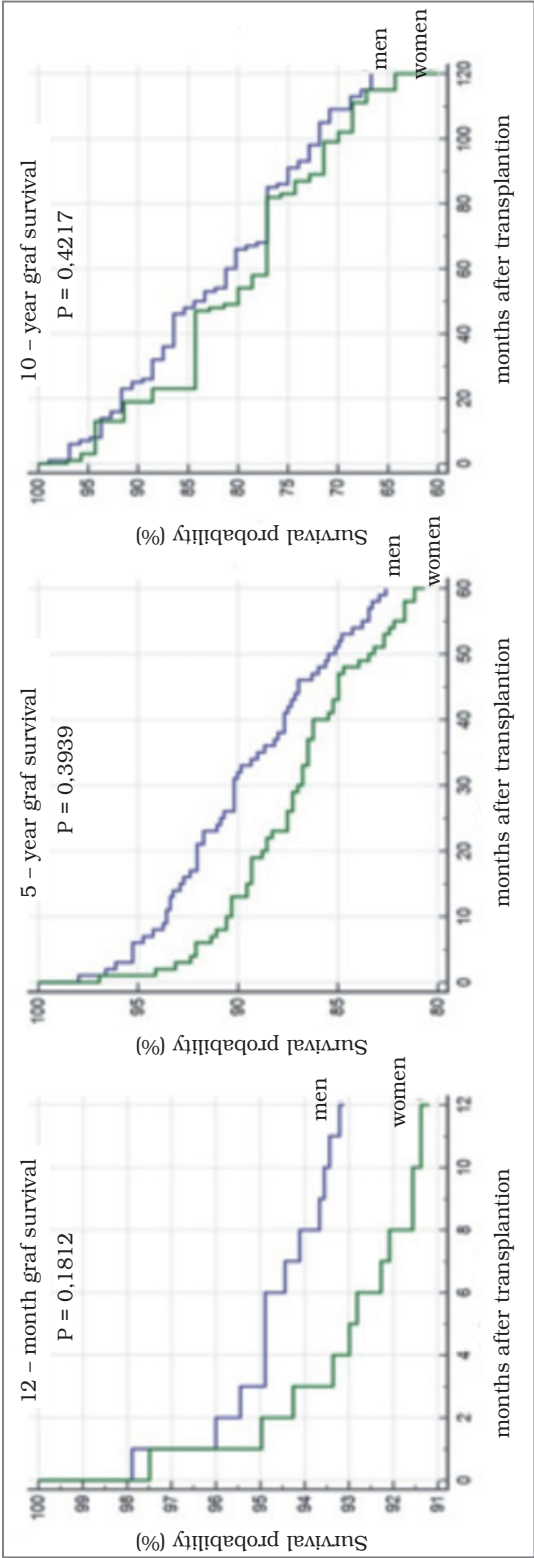


Fig. 1 Graf survival

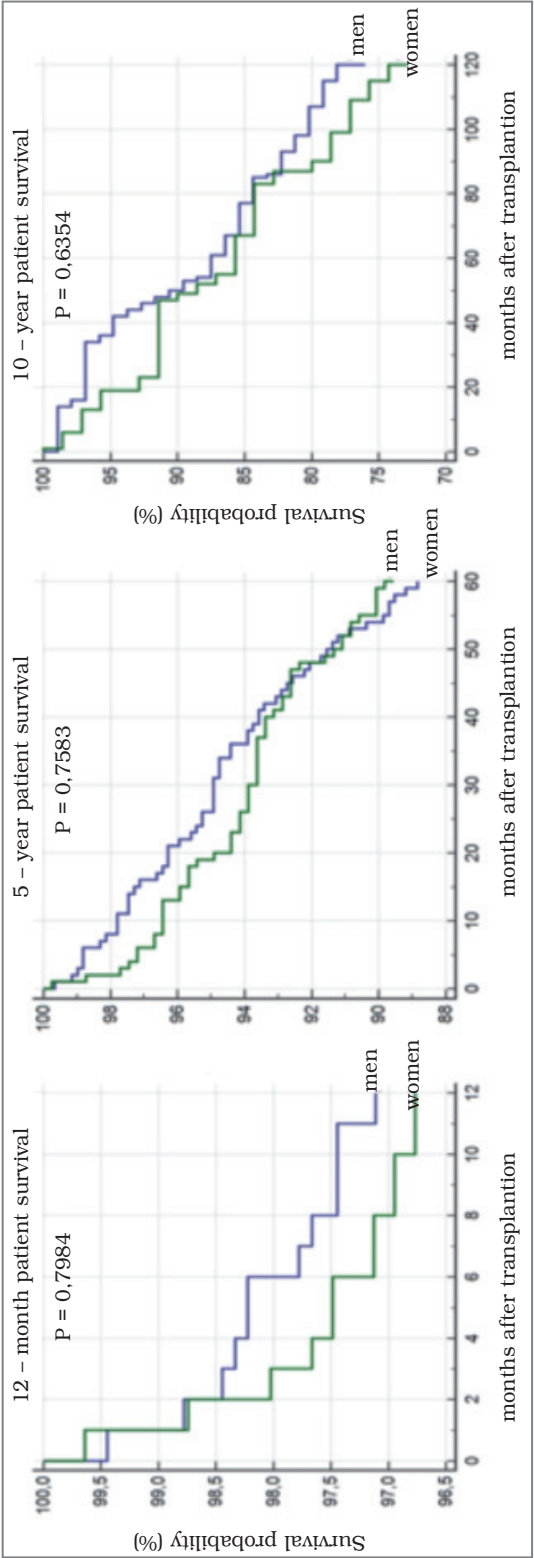


Fig. 2 Patient survival

CONCLUSION

Main limitation of our study is its retrospective character. The female recipients in our cohort waited significantly longer than the male recipients which might be due to higher PRA (Panel Reactive Antibodies) rates resulting in the lower rank in matching runs. Despite the fact we found no statistically significant difference regarding patient and graft survivals between the genders, the women had poorer outcomes than the men; mechanisms leading to such disparity call for more studies taking gender into consideration in order to minimise gender bias.

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