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KIDNEY FUNCTION DECLINE AND MORTALITY IN DONORS WITH EXPANDED CRITERIA-FIVE YEARS FOLLOW-UP STUDY

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Abstract

Kidney donors are considered healthy, but with a need for continued medical follow up and encouragement for continued healthy lifestyle, especially when expanded criteria for donation are applied. This study aims to analyse the five years follow up of kidney donors after explanation, encountering risks of kidney function decline and donors' mortality.

Material and methods:In a retrospective study we evaluated a donor cohort with 5 years of follow up. Demographic characteristics as age, gender and the presence of comorbidities as diabetes, hypertension, hyperlipidemia and Body Mass Index (BMI) >30kg/m^2 were analysed. Estimated glomerular filtration rate (eGFR) by CKD EPI formula was notified prior donation, and annually afterwards. Consultations with nephrologist or other specialists were notified. In a multivariate regression analysis, the reduction ratio (RR) of eGFR was explored as dependent variable. Cox regression analysis exploited mortality; Kaplan Meier survival curve was applied in respect of BMI.

Results:Seventy-five donors with average age above 55 years were predominantly women (69%), nearly every nineth patient had diabetes or obesity (9%). Proportion of donors referred to nephrologist at the 12 months, declined up to 58% at the fifth year, ignoring medical checks showed ascending trend to 16% at the end of second and third year and 12% at the end of observational period. The univariate regression analysis found diabetes, hyperlipidemia and hypertension, the presence of multiple comorbidities, gender and age as insignificant predictors of eGFR 12 months reduction ratio. The nephrologist referral showed borderline significance (β = - 0.103, p=0.076). Only BMI over 30kg/m^2 worsened the kidney function (β = 0.600, p=0.001). Five years mortality rate was 6.7%. The diseased donors were significantly older, more frequently had diabetes and obesity also they had significantly lower eGFR pre-donation, at the end of the first year but also and more step decline of it after 12 months. In the multivariate analysis BMI>30kg/m^2 emerged as most powerful predictor of mortality (HR: 40.02, 95% CI: [4.11-389], p=0.0001). Survival of obese patients was significantly shorter when compared with patients with lower body weight (43.28 ± 7.51 vs. 59.33±0.65, Log rank p=0.000), respectively

Conclusions: Our study demonstrates that the mortality and declination of renal function after donation are associated with nephrologist referral and other potentially modifiable factors, especially obesity. Improved protocols for pre-donation information, education and adequate after-donation follow up is mandatory to achieve better longevity and kidney function survival in these frail and precious individuals.

Key words: donors, kidney function decline, mortality, obesity, nephrologist referral

Introduction

Worldwide, constantly there is an increasing number of patients with the need of kidney transplantation, endured by the problem of donor organ shortage [1,2].

New strategies and efforts to find alternative solutions to the lack of supply of kidneys or reduce the need for kidney donation emerged not only from the altruistic but also from the economic view of this problem [3,4].

In the last decades, the number of patients that required renal replacement therapy in North Macedonia showed step rising trend [5] with still dominant living kidney over cadaveric transplantation, covering small percentage of the dialysis patients [6].

Expanded criteria for living donors as: age (elderly - above 65 years), unrelated (emotionally related), marginal and ABO incompatible living donors, are being accepted [7,8].

At hospital discharge donors are instructed for annual consultations with nephrologist and more frequently if necessary. Kidney donors are considered healthy, but recent review on long term medical outcomes emphasizes the need for continued medical follow up and encouragement for continued healthy lifestyle because, similar to general population with aging many will develop kidney and cardiovascular disease risk factors such as obesity, hypertension and diabetes (9). This study aims to analyse the five years follow up of kidney donors after explanation, encountering risks of kidney function decline and donors' mortality.

Material and methods

We retrospectively studied consecutive donor cohort from one transplant center from 2013 to 2017 with 5 years of follow up. Data were extracted from the hospital registry, the National Integrated Health Information System–My Term *Moj termin* [10].

Demographic characteristics as age, gender and the presence comorbidities as diabetes, hypertension, hyperlipidemia and Body Mass Index (BMI) >30kg/m^2 were analysed. Donors with more than two comorbidities were stratified as with multiple comorbidities. Estimated glomerular filtration rate (eGFR) by CKD EPI formula was notified prior donation, and annually afterwards. Consultations with nephrologist or other specialists were notified. Subjects with missing data in the electronic bases were contacted directly or via kidney recipients for further information. In a multivariate regression analysis, the reduction ratio (RR) of eGFR was explored as a dependent variable. Cox regression analysis exploited mortality; Kaplan Meier survival curve was applied in respect of BMI.

Results

A demographic and clinical characteristic of the study group are shown in Table 1. Seventy-five donors with average age above 55 years were predominantly women (69%). Nearly half of all had multiple comorbidities. Hypertension, as the most frequent comorbidity, was presented in 39% of donors and nearly every nineth patient had diabetes or obesity.

Table 1. Pre-donation demographic and clinical characteristics of donors

N=75	Mean ± SD / N^o (%)
Age (years)	58.80 ± 10.81
Men	23 (31%)
Diabetes	8 (10%)
Hypertension	29 (39%)
Hyperlipidemia	4 (5%)
BMI > 30Kg/m^2	7 (9%)
Multiple comorbidities	36 (48%)
eGFR (ml/min) pre-donation	94.01 ± 19.78

Kidney function follow up referral of donors to physicians by different specialty is shown on Figure 1. The vast majority of donors (83%) were referred to nephrologist at the 12 months, but this number declined up to 58% at the fifth year of follow up. The portion of donors that consulted other specialists ranged from 17 to 30 % and the number of those who ignored medical checks showed ascending trend to 16% at the end of second and third year and 12% at the end of observational period.

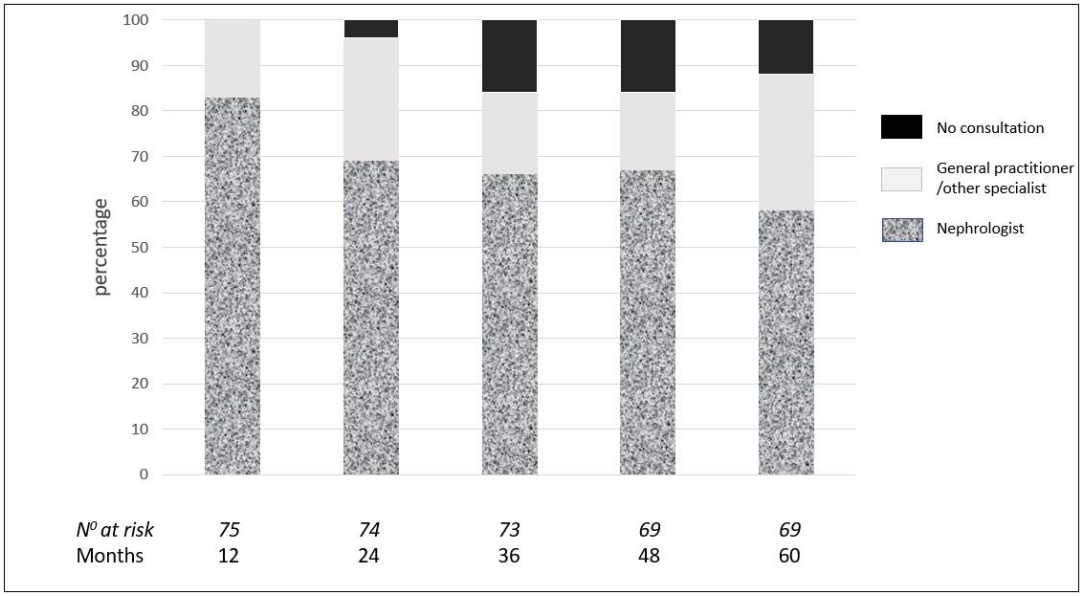

Figure 1. Annual medical referral of donors for kidney function check to nephrologist or other specialty physicians in five years follow up.

Pre-donation average eGFR was 94.01 ± 19.78 mL/min and it declined to 69.86±21.88ml/min at the end of the first, to 67.29±19.40ml/min at the second, up to 66.07±18.65ml/min at the end of the fifth year of follow up (Figure 2). The reduction ratio of eGFR was 26.40±18.93% at the end of the first year, and raised on yearly bases up to 28% at the end of the observation period.

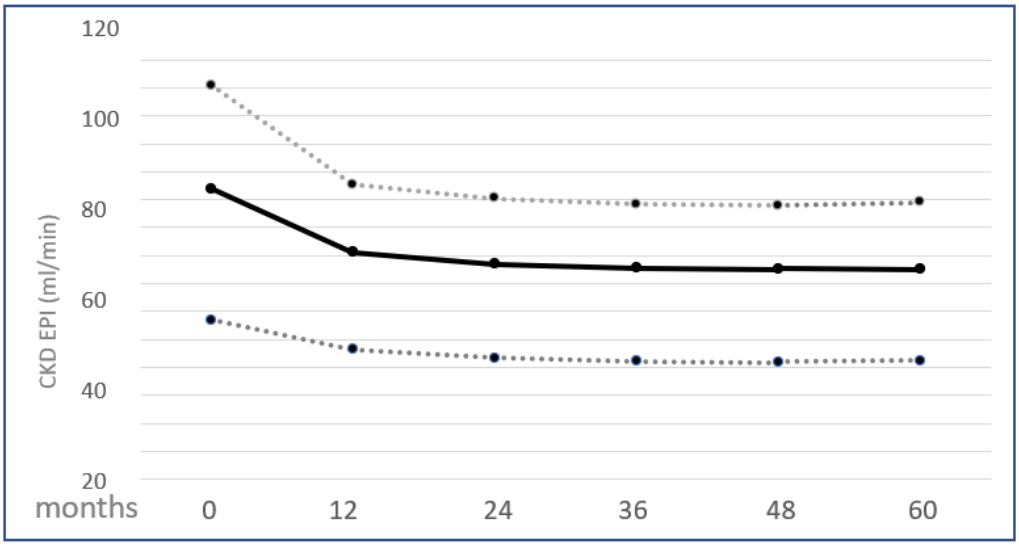

Figure 2. Renal function decline in five years after donation

The univariate regression analysis found diabetes, hyperlipidemia and hypertension, the presence of multiple comorbidities, gender and age as insignificant predictors of eGFR 12 months reduction ratio.

The nephrologist referral showed borderline significance (β = - 0.103, p=0.076). Only BMI over 30kg/m^2 worsened the kidney function (β = 0.600, p=0.001).

Five years mortality rate was 6.7%. Five donors died, one of malignant disease and four of cardiovascular disease: three cases of ischemic stroke and one of heart failure. Two donors required dialysis treatment. The diseased donors were significantly older, more frequently had diabetes and obesity (p<0.003,

p<0.029, p<0.001), respectively, also they had significantly lower eGFR pre-donation, at the end of the first year but also and more step decline of it after 12 months, as shown in Table 2.

Table 2. Comparative analysis of deceased and alive donors after 5 years in respect of demographics, comorbidities and eGFR reduction ratio.

Mortality	Alive N=70	Dead N=5	p
Age (years)	57.83±10.49	72.40±4.15	0.003
Male gender	23 (33%)	0 (0%)	0.151
Diabetes	6 (8.7%)	2 (40%)	0.029
Hypertension	26 (37%)	3 (60%)	0.289
BMI > 30 (Kg/m^2)	3 (4.3%)	4 (80%)	0.001
Hyperlipidemia	4 (5.7%)	0 (0%)	0.759
Multiple comorbidities	23 (33%)	23 (33%)	0.461
eGFR (ml/min) pre-donation)	95.68±18.59	67.00±21.41	0.004
eGFR (ml/min) 12 months	72.25±19.49	31.33±15.94	0.001
Reduction ratio 12month	24.11±17.53	55.50±5.9	0.001

The lower pre-donation eGFR, the presence of diabetes, obesity and advanced age increased the risk of mortality in the univariate Cox-regression analysis (p=0.045, p=0.053, p=0.001, p=0.012, respectively), as shown in Table 3.

Table 3. Univariate Cox-regression mortality analysis-variables with significant Hazard Ratio

variable	Hazard ratio	Confidential interval	p
eGFR pre-donation (< 77 ml/min)	6.22	1.039-37.24	0.045
Diabetes	5.84	0.975-35.088	0.053
BMI > 30 (Kg/m^2)	49.5	5.49-445.90	0.001
Age > 65 years	9.97	1.663-59.82	0.012

BMI – Body mass index, eGFR of 77ml/min value for cut-off as third percentile

In the multivariate analysis BMI>30kg/m^2 emerged as most powerful predictor of mortality (HR:40, 95 CI: [4.11-389], p=0.0001). Donors with obesity were forty times more at risk of dying than non obese ones. Survival of obese patients was significantly shorter when compared with patients with lower body weight (43.28 ± 7.51 vs. 59.33±0.65, Log rank p=0.000), respectively, (Figure 3).

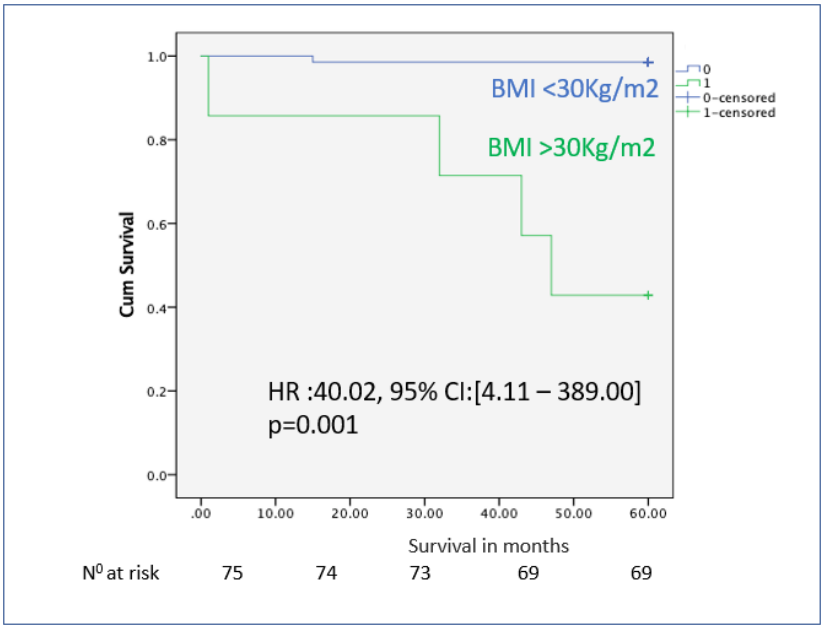

Figure 3. Kaplan Meier survival of donors in respect of BMI

Discussion

Kidney donors' eligibility encounters willing healthy individuals who are intended and expected not to be harmed by the process of donation, especially in respect of the donor's kidney function and overall survival.

The expanded criteria and inclusion of marginal donors triggered the need of profound scientific research elucidating factors that compromise those outcomes. Our study included donors with age above 65 years, well controlled nonproteinuric diabetes, hypertension and BMI up to 35kg/m^2. The 5 years overall mortality rate was 6.7% which was comparable to 4,2% mortality in the study by Segev at al. [11].

The predictors of mortality comprised of advanced age, diabetes and obesity which are already being well recognized as survival worsening factors (12-14). A large survey of transplant centers found the BMI threshold of 35 kg/m^2 in more of half of the centers, while 10% of programs decline donors with a BMI of >30 kg/m^2 [15].

In our donor's population near 10% were obese, similar to Reese study where 17.8% of donors were explanted with BMI of 30-35 kg/m^2 [16].

The diseased donors also had lower pre-donation eGFR and more rapid declination of kidney function. Since they were also almost all obese, we might explain the overlapping phenomenon of the two confounding factors in the declination of the kidney function and survival. When kidney donors present with minimal kidney reserve, the hypertension and obesity as part of the metabolic syndrome aggravate declination of kidney function after donation [17].

Most of studies that did research on survival and eGFR after donation in obese subjects failed to prove worse short follow up outcomes compared to non-obese donors [18-20].

In contradiction, Quadri et al suggest that the concurrent hypertension and obesity have major and additive adverse impact on compensatory GFR rise in living donors over 5 years [21].

Strict follow up of donor's health, especially in the group of marginal and donors of expanded criteria and the need of nephrologist referral are mandatory by most of the recommendations [22-24].

In our analysis we included the data on annual nephrologist referral. Nearly halved portion of patients did not consult nephrologist at the fifth year of follow up and nearly 16% ignored medical check at all. In Reese's study [16] 61% of donors did not have adequate follow up at the first year and medically more complex donors had better follow up.

As a predictor of kidney function decline, the nephrologist non-referral emerged as important risk factor in our analysis, but lost the significance in the final model where obesity had overridden all other risk factors.

This fact elucidates the need of a structured program for follow up of donors, especially of those with expanded criteria. Future, donors that are already obese should be informed and advised of the need of losing weight, and also after donation to lead a healthy life style emphasizing the possible deterioration of kidney function. In order to do an adequate, follow up, donors should be informed and advised for regular nephrologist check.

There are several limitations considering this study. It's a retrospective study; some of the data wasn't retrieved out from the national data system but by telephone contact.

For several patients there was missing data and despite of the repeated attempts we failed to contact one donor. The patients follow up wasn't complete and data about other known risk factors for kidney function decline as for example smoking, dietary habits, lack of health insurance, distance from nephrologist center and etc, were not obtained.

Conclusions

Our study demonstrates that the proportion of donors that are not adequately followed is high.

The mortality and declination of renal function after donation are associated with nephrologist referral and other potentially modifiable factors, especially obesity. Improved protocols for pre-donation information, education and adequate after-donation follow up are mandatory to achieve better longevity and kidney function survival in these frail and precious individuals.

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