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**ORIGINAL ARTICLE**

# Determining kidney function before and after kidney donation in living kidney donors: single-centre experience

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## ABSTRACT

**Aim** The most common type of kidney transplantation in Bosnia and Herzegovina is from living donors, but there is a lack of published data on glomerular filtration rate (GFR) values and kidney outcomes in living kidney donors. This study aimed to evaluate the safety of living kidney donation at our centre.

**Methods** One hundred and seventy living kidney donors at the University Clinical Centre Tuzla were analysed. Initially, there were 170 participants; however, only 31 provided all the required medical data and completed the study. GFR was estimated (eGFR) using the CKD-EPI and MDRD formulas, and a web-based calculator was used to predict GFR > 90 ml/min/1.73 m², along with measurement of creatinine clearance (CrCl). Measured GFR (mGFR) was assessed through technetium-99m diethylene triamine pentaacetic acid (DTPA) renogram, with follow-up visits to estimate post-donation GFR.

**Results** The CKD-EPI, MDRD, and web-based application showed similar diagnostic performances, with MDRD and CKD-EPI systematically underestimating mGFR. CrCl demonstrated strong diagnostic performance. Follow-up visits showed that most donors had post-donation eGFR values between 45 and 89 mL/min/1.73 m², with none progressing to pre-dialysis or the dialysis stage after kidney donation.

**Conclusion** CrCl demonstrated strong diagnostic performance in our study population, and the DTPA renogram reliably assessed kidney function. Post-donation eGFR levels were satisfactory, indicating that our diagnostic workup for potential living kidney donors in our centre is safe and effective.

**Keywords:** glomerular filtration rate, kidney transplantation, organ donation

## INTRODUCTION

”Primum non nocere” is one of the fundamental principles in medicine, including kidney transplantation. In the context of living kidney donation, this principle highlights the importance of ensuring the health and well-being of living kidney donors after they donate. This is especially important in countries like Bosnia and Herzegovina (B&H), where the pool of donated kidneys mainly comes from living donors (1).

Kidney function is determined through glomerular filtration rate (GFR), which can be estimated (eGFR) or measured (mGFR). Formulas for the estimation of GFR are the most commonly used tool for determining kidney function. However, they come with problems such as dependency on serum creatinine, whose level is affected by many 'non-renal factors' such as muscle mass, diet, and dietary supplements. Formulas offer the possibility of combining serum creatinine and cystatine C levels; however, cystatine C levels are affected by inflammation, malignancy, thyroid disorders, diabetes, certain drugs like corticosteroids, and smoking (2). Measuring GFR is considered the gold standard for kidney function evaluation, and it can be done using exogenous or endogenous markers. 24-hour creatinine clearance is a method of measuring GFR using creatinine, but it can be affected by mistakes in collecting the 24-hour urine. mGFR with exogenous marker is considered to be a gold standard; however, these methods are not always readily available, especially in developing countries, and require more labour compared to eGFR (2–4).

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In 2016, Huang et al. developed a tool designed to assist transplant centres in estimating the likelihood that a potential donor will have a mGFR above or below specific thresholds. The probabilities used to create this tool were derived from large cohorts, including the National Health and Nutrition Examination Survey (NHANES) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (5). The effectiveness of the web application for potential living kidney donors was assessed by Gaillard et al. (6). Despite being referenced in important living kidney donor guidelines, such as the KDIGO guidelines, the tool did not achieve widespread adoption (7).

After a kidney donation, the remaining kidney compensates by increasing its function. By three months post-donation, the clearance of the remnant kidney typically increases to a mean GFR of about 65-75% of the kidney function before donation. In 22 studies that reported on this, the average decrease in GFR after donation was 26 mL/min/1.73m² (8–10).

Despite a reduction in GFR following kidney donation, the occurrence of end-stage kidney disease (ESKD) in living kidney donors is similar to, or even lower than that seen in the general population. However, the absolute risk for younger donors, as they have more time to develop these conditions, especially those with additional risk factors for ESKD, such as blood relation to the recipient, obesity, hyperlipoproteinemia, glucose intolerance, or diabetes, is likely to be more significant over their lifetime (11–13).

Currently, there are no published data concerning GFR values both before and after kidney donation of living kidney donors in B&H. To address this gap, we conducted a study aimed at providing evidence regarding the safety of living kidney donation in our country.

## PATIENTS AND METHODS

### Patients and study design

This cohort study was conducted on living kidney donors at the Department of Nephrology, Dialysis and Kidney Transplantation at the University Clinical Centre Tuzla during the period between September 1999 and September 2023. Initially, our study included 170 participants, of whom 31 were not lost to follow-up and had all the required medical data, and they remained in our study as study participants.

The study was approved by the Ethics Committee of the University Clinical Centre Tuzla.

### Methods

All living kidney donors who participated in the study underwent two methods of measuring GFR before potential kidney donation. One method of measurement used endogenous marker (creatinine clearance) (2–4), while the other used exogenous marker, 99mTc-DTPA (Technetium-99m diethylenetriaminepentaacetic acid) renal dynamic imaging (Gates' method) (2–4).

24-hour urine volume for creatinine clearance measurement was collected in a hospital setting at the Department of Nephrology, Dialysis, and Transplantation, and adjusted for body surface area. All potential kidney donors were advised on proper hydration before undergoing diethylenetriaminepentaacetic (DTPA) renogram and received an intravenous injection of 5 millicuries of 99mTc DTPA as a bolus. Images were captured from the posterior aspect using a General Electric Dual Head SPECT Gamma Camera (GE Medical Systems Millennium MG, USA). The patients' age, height, and weight data were entered into XELERIS Software, which automatically calculated the GFR. This value was then adjusted for body surface area using the DuBois formula (2). The CKD-EPI (2) and MDRD (2) formulas were utilized to estimate the GFR before considering kidney donation. Serum creatinine concentrations were measured using the Jaffe method on Advia, Beckman Coulter, and Siemens Dimension haematology analysers (Siemens Health Care, Japan) at the central laboratory of the University Clinical Centre Tuzla. A web-based application accessible at http://ckdepi.org/equations/donor-candidate-gfr-calculator/ was used to determine the probability that the mGFR is higher than 80 mL/min per 1.73 m². Living kidney donors were called for follow-up visits after kidney donation, when their GFR was estimated using the CKD-EPI formula.

### Statistical analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. Data were presented as mean±SD for normally distributed variables, and median (IQR) for non-normal distributions. As mGFR was non-normally distributed, non-parametric methods were applied for paired comparisons using the Wilcoxon signed-rank test. Associations between mGFR and eGFR methods (CKD-EPI, MDRD, and normalized creatinine clearance) were evaluated using Spearman's rank correlation. Pearson correlation and Kendall's $\tau$ were additionally calculated as sensitivity analyses. Agreement between methods was assessed using Bland–Altman analysis. Bias was defined as the mean difference (eGFR − mGFR). When differences deviated from normality, non-parametric limits of agreement ($2.5^{th}$–$97.5^{th}$ percentiles) were calculated in addition to conventional limits (mean ± 1.96 SD). Proportional bias was examined using linear regression of the Bland–Altman differences against the mean of paired measurements. For creatinine clearance, robustness of proportional bias was further assessed using leave-one-out sensitivity analysis. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

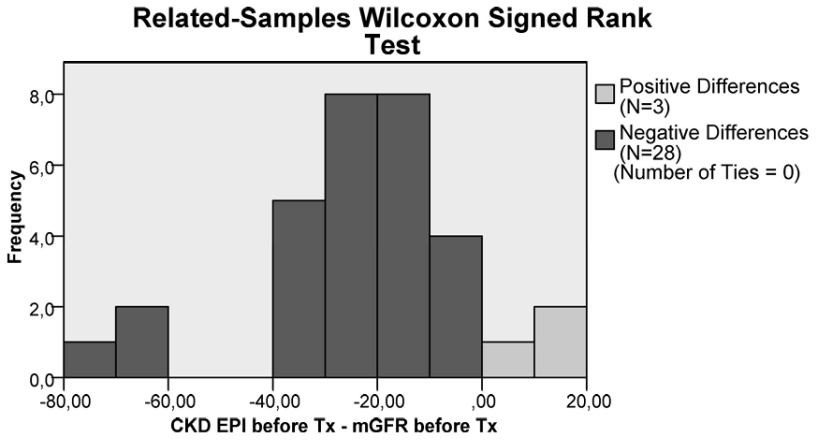
## RESULTS

The study included a total of 31 participants, of whom 19 (61.3%) were women and 12 (38.7%) were men.

The mean age at the time of kidney donation was 52.6 ± 8.01 (range 35–68) years (normal distribution) confirmed by the Shapiro Wilk test ($p = 0.841$). Mean serum creatinine was 73.03 ± 11.49 µmol/L (range 47–96), and values were normally distributed ($p = 0.926$). The measured GFR (mGFR) was not normally distributed ($p = 0.009$). The median mGFR was 112.09 mL/min/1.73 $m^2$ (IQR 20.71), ranging between 85.8 to 171.02 mL/min/1.73 $m^2$. Mean creatinine clearance was 115.62 ± 29.92 mL/min (range 73.8–187.8), with normal distribution confirmed ($p = 0.126$). The mean CKD-EPI was 94.03 ± 13.6 mL/min/1.73 $m^2$ (range 66–117), and the mean MDRD-estimated GFR was 84.65 ± 16.64 mL/min/1.73$m^2$ (range 51–114). Both variables were normally distributed ($p = 0.646$ and $p = 0.535$, respectively).

**Comparison of mGFR with CKD EPI before kidney donation.** Because at least one variable (mGFR) was non-normally distributed, non-parametric methods were applied for paired comparisons.

The Wilcoxon signed-rank test demonstrated statistically significant difference between mGFR and CKD-EPI (n = 31, Z = -




| | |
|---|---|
| **Total N** | 31 |
| **Test Statistic** | 17,000 |
| **Standard Error** | 51,029 |
| **Standardized Test Statistic** | -4,527 |
| **Asymptotic Sig. (2-sided test)** | ,000 |

**Figure 1. Wilcoxon paired samples test of measured glomerular filtration rate (mGFR) and Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula**

4.53; p < 0.001). In 28 of 31 cases, CKD-EPI values were lower than mGFR, indicating systematic underestimation bias (Figure 1).

Spearman's rank correlation analysis demonstrated a statistically significant, moderate positive association between mGFR and CKD-EPI values before kidney donation (ρ = 0.405; p = 0.024).

The Bland–Altman analysis showed mean difference-bias of –22.0 mL/min/1.73 m$^2$, indicating systematic underestimation of CKD-EPI relative to mGFR (Figure 2). As the paired differences were not normally distributed, non-parametric limits of agreement were calculated using the 2.5$^{th}$ and 97.5$^{th}$ percentiles ranging from –70.4 to 11.2 mL/min/1.73 m².

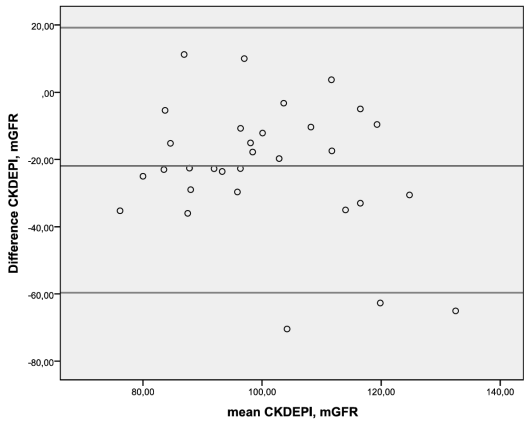



**Figure 2. Bland-Altman plot showing agreement between Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and measured glomerular filtration rate (mGFR)**

Linear regression analysis of the Bland–Altman differences revealed no proportional bias. The association between the mean GFR and the difference (CKD-EPI – mGFR) was weak and not statistically significant (R = 0.268, R$^2$ = 0.072; p = 0.145). The regression slope was negative and non-significant (B = –0.361; p = 0.145), indicating that the magnitude of underestimation did not significantly vary across the range of GFR values.

**Comparison of mGFR with MDRD before kidney donation.** As the mGFR variable was not normally distributed, non-parametric methods were applied for paired comparisons. The Wilcoxon signed-rank test showed a statistically significant difference of mGFR and MDRD (N = 31; Z = -4.80; p < 0.001). In 29 of 31 cases, MDRD values were lower than mGFR, indicating systematic underestimation.

The Spearman's rank correlation demonstrated a moderate, statistically significant positive association between mGFR and MDRD values (ρ = 0.416; p = 0.020). Bland-Altman analysis demonstrated a mean difference (bias) of –31.42 mL/min/1.73 m$^2$, indicating substantial underestimation of mGFR by MDRD (Figure 3). The limits of agreement were wide, from –71.91 to 9.07 mL/min/1.73 m$^2$. Linear regression analysis of the Bland-Altman differences demonstrated no evidence of proportional bias. The association between the mean GFR and the MDRD – mGFR was weak and not statistically significant (R = 0.112, R$^2$ = 0.012; p = 0.550). The regression slope was not statistically significant (B = -0.162; p = 0.550), indicating that the degree of underestimation by MDRD did not significantly vary across the range of GFR values.

**Comparison of mGFR with normalized creatinine clearance before kidney donation.** Because the mGFR variable

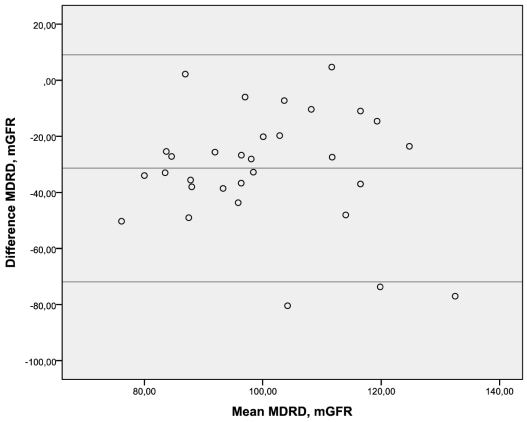



**Figure 3. Bland-Altman plot showing agreement between Modification of Diet in Renal Disease (MDRD) formula and measured glomerular filtration rate (mGFR)**

was not normally distributed, non-parametric methods were applied for paired comparisons. Creatinine clearance values were normalized to body surface area (mL/min/1.73 m²). The Wilcoxon signed-rank test showed no statistically significant difference between normalized creatinine clearance and mGFR (Z = -1.25; p = 0.21), indicating no evidence of systematic bias (Figure 4). Spearman's rank correlation demonstrated a moderate positive association between normalized creatinine clearance and mGFR (ρ = 0.447; p = 0.012), indicating that higher creatinine clearance values were associated with higher mGFR values. Bland-Altman analysis showed a mean difference of -6.79 mL/min/1.73 m² (SD = 26.9), indicating minimal average bias between the methods. The limits of agreement ranged from –59.51 to 45.93 mL/min/1.73 m², reflecting substantial variability at the individual level.

Linear regression of the Bland-Altman differences revealed evidence of proportional bias. The association between the mean GFR and the CrCl – mGFR was moderate and statistically significant (R = 0.393, $R^2$ = 0.154; p = 0.029). The positive regression slope (B = 0.555; p = 0.029) indicates that the difference between methods increased with higher GFR values, suggesting that creatinine clearance tends to overestimate mGFR at higher levels of kidney function (Figure 5).

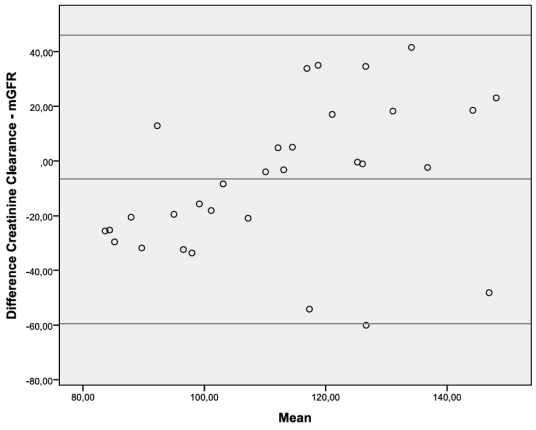
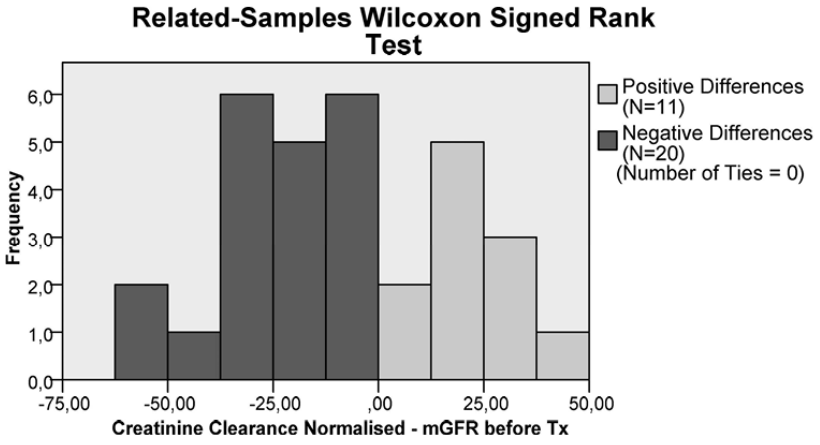



**Figure 5. Bland-Altman plot showing agreement between normalized creatinine clearance and measured glomerular filtration rate (mGFR**

**Comparison of mGFR and post-test probability for GFR > 90 before kidney donation.** Spearman's rank correlation analysis showed a weak positive association between mGFR




| | |
|---|---|
| **Total N** | 31 |
| **Test Statistic** | 184,000 |
| **Standard Error** | 51,029 |
| **Standardized Test Statistic** | -1,254 |
| **Asymptotic Sig. (2-sided test)** | ,210 |

**Figure 4. Wilcoxon paired samples test of measured glomerular filtration rate (mGFR) and creatinine clearance**

and the post-test probability of GFR > 90 before kidney donation (N = 31; ρ = 0.213; p = 0.251). However, this association did not reach statistical significance, indicating that post-test probability was not significantly correlated with measured GFR in this cohort.

**GFR after kidney donation.** At follow-up, most donors (N = 27) had a post-donation eGFR of 45–89 ml/min/1.73 $m^2$. One donor had an eGFR ≥ 90 ml/min/1.73 $m^2$, while three donors had values between 30 and 44 ml/min/1.73 $m^2$. No donor had an eGFR < 30 ml/min/1.73 $m^2$.

**Sensitivity analysis.** Correlation analyses were repeated using Pearson correlation and Kendall's τ as sensitivity significance and magnitude varied slightly, likely reflecting the limited sample size. Overall interpretation of weak-to-moderate associations did not change. Bland-Altman bias and limits of agreement were recalculated using both conventional parametric limits (mean ± 1.96 SD) and non-parametric percentile limits ($2.5^{th}$ and $97.5^{th}$ percentiles). Differences between approaches were minimal and did not affect interpretation of systematic bias. Proportional bias for CrCl was additionally evaluated using a leave-one-out sensitivity analysis. Across 31 re-estimated models, regression slopes remained positive (B range 0.516 – 0.776), and statistical significance was preserved in the majority of re-estimations (range p = 0.002 – 0.058), indicating that the observed proportional bias was not driven by single influential observations.

## DISCUSSION

We have evaluated two methods of GFR estimation, CKD-EPI and MDRD, and a web-based calculator for predicting mGFR, as well as CrCl as a method of mGFR using an endogenous marker. These were compared with the DTPA renogram, the only available method for measuring GFR using an exogenous marker at our centre and in our country. Our findings indicated that CKD-EPI, MDRD, and the web-based application had similar diagnostic performance in terms of agreement with mGFR values. Both MDRD and CKD EPI systematically underestimated mGFR in our study population. Also, no significant association between post-test probability GFR >90 and mGFR values before kidney donation was demonstrated. On the other hand, CrCl performed the best, showing no systemic disagreement with mGFR values, a notable distinction compared to the other methods.

Traditionally, it is thought that creatinine clearance is not precise enough due to potential errors in 24-hour urine collection (14,15). However, since urine collection was conducted in a hospital setting by well-trained personnel, the likelihood of technical errors in our study was minimal. Also, CrCl tend to overestimate mGFR due to distal tubular creatinine secretion (14,15). Neetika et al. recommended the CER4 formula developed by Ix et al. as the preferred method for assessing the accuracy of timed urine collections and CrCl in potential donors, due to its demonstrated reliability in their study (15).

In a 2007 survey of living kidney transplant programs in the United States, 90% used 24-hour CrCl to assess GFR (16). Similarly, a survey in 28 transplant centres in Argentina indicated that 78.5% also relied on 24-hour CrCl to assess kidney function in potential donors (15). In a study involving multiple cohorts from transplant centres in the Netherlands, the authors recommended using 24-hour CrCl and/or eGFR as sufficient for donor selection in most potential donors, as they found no significant increase in acceptance rates when using mGFR with an exogenous marker (17). They also did not observe any differences in eGFR five-year post-donation between centres using eGFR and those utilizing mGFR-based screening (17).

Data on DTPA renogram – the reference method for mGFR with an exogenous marker in our study, are relatively scarce in the recent literature (2). As a radionuclide measurement method for GFR, the DTPA renogram is generally regarded as less valuable and less accurate than urinary and plasma clearance procedures (2). However, in our experience, it is a reliable method for determining kidney function, with a significant advantage over plasma or urinary clearance methods, as it provides data on split-kidney function when indicated.

A comprehensive evaluation before living kidney donation helps explain findings from numerous studies indicating that the remaining kidney function of living donors remains stable for months and years following transplantation (18–20). Additionally, these studies show that kidney donation does not significantly increase the risk of developing ESKD (18–20). Our study supports these findings, revealing that most living kidney donors in our population had post-donation eGFR between 45 and 89 mL/min/1.73 m², and none had a post-donation eGFR below 30 mL/min/1.73 m², even with only one kidney remaining and being of older age. It is important to highlight that none of the living kidney donors progressed to the pre-dialysis or dialysis stage following their kidney donation. This demonstrates the thorough diagnostic evaluation of donors prior to donation and the high safety standards of living kidney transplantation in our centre.

Our study had some limitations, primarily due to the relatively small number of participants. However, all participants had available data on eGFR, CrCl, the web-based calculator, and mGFR before kidney donation, as well as eGFR after kidney donation.

In conclusion, this is the first study to examine GFR values before and after kidney donation among living kidney donors in Bosnia and Herzegovina. We found that measuring CrCl is a safe, easy, accessible, and cost-effective method for measuring GFR in potential living kidney donors. Additionally, the reliability of the DTPA renogram for kidney function assessment was confirmed, and we emphasize its utility in determining split kidney function. We also found satisfactory eGFR levels after kidney donation. Overall, this enabled us to conclude that our diagnostic workup for potential living kidney donors at our centre is safe and effective. We believe our experience may benefit other resource-limited centres facing similar challenges in balancing locally available methods with what is considered mandatory in well-resourced healthcare systems.

## FUNDING

No specific funding was received for this study.

## CONFLICTS OF INTEREST

None to declare.

## ETHIC STATEMENT

The study was approved by the Ethics Committee of the University Clinical Centre Tuzla (approval number 02-09/2-32/23; date: May 10, 2023).

## DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request and with permission of the institution.

## AUTHOR CONTRIBUTIONS (CRediT)

**Conceptualization:** M.P., M.A.-H., E.Z.; **Data curation:** M.P., M.A.-H., E.Z.; **Formal analysis:** M.P., M.A.-H., E.Z.; **Investigation:** M.P., E.Z., A.K., N.M., I.Č., A.J., M.B.-D., S.H., M.D.-T., B.I., M.S.; **Methodology:** M.P., M.A.-H., E.Z.; **Supervision:** M.A.-H.; **Visualization:** E.Z.; **Writing – original draft:** M.P., M.A.-H., E.Z.; **Writing – review & editing:** M.P., M.A.-H., E.Z. All authors have read and agreed to the published version of the manuscript.

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