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Performance of the New CKD-EPI Creatinine- and Cystatin C–based Glomerular Filtration Rate Estimation Equation in Living Kidney Donor Candidate

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Background. Accurate preoperative evaluation of renal function in living kidney donor candidates (LKDCs) is crucial to prevent kidney failure after nephrectomy. We examined the performance of various estimated glomerular filtration rate (eGFR) equations, including the new chronic kidney disease epidemiology collaboration (CKD-EPI) equation in LKDCs. **Methods.** We analyzed 752 LKDCs who were assessed for measured GFR by inulin clearance as part of routine pretransplant examination from 2006 to 2020. CKD-EPI2012 from cystatin C (CKD-EPI12cys), CKD-EPI2021 from creatinine (CKD-EPI21cr), CKD-EPI21cr-cys, Japanese modified (JPN) eGFRcr, and JPN eGFRcys were compared in determining the suitability for LKDCs. **Results.** CKD-EPI12cys had the lowest absolute and relative biases, with higher P_{30} and P_{10}, followed by JPN eGFRcys, CKD-EPI21cr, and CKD-EPI21cr-cys. The root mean square error was least for CKD-EPI12cys, then JPN eGFRcys, CKD-EPI21cr-cys, CKD-EPI21cr, and JPN eGFRcr. CKD-EPI21cr, CKD-EPI12cys, and CKD-EPI21cr-cys estimated GFR higher, whereas JPN eGFRcr estimated GFR lower. At the threshold of 90 mL/min/1.73 m^2, CKD-EPI21cr had the highest percentage of misclassification at 37.37%, whereas JPN eGFRcr had the lowest percentage of misclassification at 6.91%. Using the age-adapted approach, JPN eGFRcr had the lowest percentage of misclassification into overestimation at 7.31%. All eGFR had >5.0%, and CKD-EPI21cr had the highest percentage of misclassification at 21.94%. Conversely, CKD-EPI21cr-cys had the lowest percentage of misclassification into underestimation at 3.19%, both at the threshold of 90 mL/min/1.73 m^2 and the age-adapted approach. JPN eGFRcr had the highest percentage at 33.38% and 40.69%, respectively. **Conclusions.** In evaluating the renal function of Japanese LKDCs, the new CKD-EPI equation had a lower rate of underestimation but a relatively high rate of overestimation. New GFR estimation formulas are needed to be tailored to each ethnic group to enhance the accuracy and reliability of donor selection processes.

(*Transplantation Direct* 2024;10: e1712; doi: 10.1097/TXD.0000000000001712.)

Received 23 April 2024. Revision received 29 July 2024.
Accepted 31 July 2024.
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The authors declare no funding or conflicts of interest.
Y.K. participated in research design, writing the article, performing the research, and data analysis. Y.M.-H. participated in research design. S.M., S.F., and R.T. participated in research design and data analysis. H.Y., S.N., and K.Y. participated in research design, performing the research, and data analysis. Y.I. and N.N. participated in research design, performing the research.
Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).
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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001712

Evaluation of renal function in potential living kidney donors is crucial for the success of living kidney transplantation. Compared with deceased transplantation, living kidney transplantation has several advantages to the recipients, including higher HLA compatibility, lower frequency of delayed graft function, and higher graft survival rates.[1] Conversely, it has the disadvantage of removing a kidney from a healthy donor, and it is important to carefully consider the potential risks associated with kidney donation for each donor. The evaluation process for potential living kidney donors encompasses various tests, with renal function assessment being paramount. According to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline, the initial assessment is made by estimating glomerular filtration rate (GFR) from serum creatinine, and donor GFR should be confirmed using ≥1 of the following measurements: measured GFR (mGFR) using exogenous filtration marker, creatinine clearance, estimated GFR (eGFR) from the combination of serum creatinine and cystatin C, and repeat eGFR from serum creatinine.[2] According to the same guidelines, a GFR of ≥90 mL/min/1.73 m^2 is considered an acceptable level

for a donor, and a GFR of <60 mL/min/1.73 m² is considered not indicated for a donor. In the British Transplantation Society (BTS) guideline, the assessment method is almost the same as in KDIGO, but the recommended threshold levels differ by sex and age.[3] The European renal best practice transplantation guideline also recommends age-specific GFR threshold levels.[4,5] In any case, efforts must be made to accurately assess the potential donor's renal function and ensure that the donor will not suffer from chronic kidney disease (CKD) or other diseases after renal transplantation and that both the donor and the recipient will have long-term survival.

The gold standard method of assessing GFR is the measurement of inulin clearance (Cin). However, the test is complicated and cannot be performed at all facilities. Other methods of GFR evaluation using exogenous tracers include urinary or plasma clearance of iothalamate, urinary or plasma clearance of 51Cr-EDTA, urinary or plasma clearance of iohexol, or urinary clearance of 99mTc-DTPA. Using those mGFRs, various GFR estimation formulas have been developed during the past 20 y. eGFR is a simple and efficient method to help assess the risk of CKD in patients with risk factors, such as diabetes, hypertension, and cardiovascular disease, and to follow-up with patients with CKD. The creatinine-based eGFR formula is widely used in routine clinical practice. The serum cystatin C–based formula is recommended for confirmatory testing of eGFR, although it is not yet widely used. Recently, a new creatinine- and cystatin C–based CKD-EPI2021 equation that does not consider ethnicity has been developed.[6] However, the utility of this equation in living donor candidates for renal transplantation is unknown. Moreover, it is known that the modification of diet in renal disease (MDRD) and CKD epidemiology collaboration (CKD-EPI) equations are not applicable to Asians, including Japanese; therefore, a Japanese version of the creatinine- or cystatin C–based GFR estimation equation was developed.

This study investigates the reliability of these formulas as screening alternatives to mGFR for evaluating potential living kidney donors, aiming to enhance the transplantation process's safety and efficiency.

MATERIALS AND METHODS

We analyzed 752 living kidney donor candidates (LKDCs) who were assessed for mGFR by Cin as part of routine pretransplant examination at 2 centers in Osaka University Kidney Transplant Group from 2006 to 2020. Among the participants, there are individuals who were deemed ineligible as donors because of low mGFR. The LKDCs were also measured for serum creatinine and cystatin C on the same day as Cin.

The method of measuring Cin has been described previously.[7] Briefly, LKDCs refrained from eating before the examination, and a 2-h continuous intravenous infusion of 1% inulin was administered with varying infusion rates. Blood and urine samples were collected at specified intervals. The candidates were hydrated to maintain urine flow. Cin was determined by enzymatic methods, and the mean of 3 values was used as the standardized mGFR for a body surface area of 1.73 m². Creatinine was measured by enzymatic methods. Serum cystatin C was measured using nephelometric immunoassay (Siemens) and calibrated to the standardized value traceable to ERM-DA471/IFCC using an equation reported previously.[8]

The eGFR (mL/min/1.73 m²) was calculated using the following equation:

CKD-EPI12cys: $133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age}$ (× 0.932 if woman)[9]

CKD-EPI21cr: $142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if woman], where: $\kappa = 0.7$ (women) or 0.9 (men), $\alpha = -0.241$ (woman) or -0.302 (man)[6]

CKD-EPI21cr-cys: $135 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-0.544} \times \min(S_{cys}/0.8, 1)^{-0.323} \times \max(S_{cys}/0.8, 1)^{-0.778} \times 0.9961^{Age} \times 0.963$ (if woman), where $\kappa = 0.7$ (women) or 0.9 (men), $\alpha = -0.219$ (woman) or -0.144 (man)[6]

JPN eGFRcr: $194 \times Scr^{-1.094} \times Age^{-0.287} \times 0.739$ (if woman)[7]

JPN eGFRcys: $96 \times Scys^{-1.324} \times 0.996^{Age} \times 0.894$ (if woman)[8]

Scr is serum creatinine, and Scys is serum cystatin C. Min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

This study was approved by the appropriate research ethics committee (approval No.: 21375) and conducted according to the Declaration of Helsinki. All participants provided written informed consent.

All data were collected and analyzed on November 30, 2023, using the Research Electronic Data Capture electronic registration software (Vanderbilt University, Nashville, TN). Each equation was evaluated by absolute and relative bias, root mean square error, and accuracy within 30% (P_{30}) and 10% (P_{10}). The performance of each GFR estimation formula was evaluated to determine mGFR ≥90 mL/min/1.73 m² and age-adapted thresholds, according to the BTS guidelines[3] (**Table S1, SDC,** http://links.lww.com/TXD/A701).

RESULTS

Patient Background

The study participants comprised 465 men (61.83%) and 287 women (38.16%). Their age, height, weight, body mass index, and mGFR were 59.01 ± 11.22 y, 160.73 ± 8.91 cm, 59.39 ± 11.05 kg, 22.88 ± 3.13. kg/m², and 90.88 ± 17.29 mL/min/1.73 m², respectively. Their CKD-EPI12cys, CKD-EPI21cr, CKD-EPI21cr-cys, JPN eGFRcr, and JPN eGFRcys were 95.61 ± 16.49, 99.64 ± 14.07, 100.98 ± 15.71, 78.13 ± 19.33, and 95.61 ± 16.49 mL/min/1.73 m², respectively.

Performance of Each Equation

Table 1 shows the performance of each equation, with CKD-EPI12cys having the lowest absolute bias of 1.76 (95% confidence interval [CI], 0.67-2.87) and a relative bias of 3.48% (95% CI, 2.17-4.80). The JPN eGFRcys had an absolute bias of 3.24 (95% CI, 2.80-3.70) and a relative bias of –2.35% (95% CI, –3.63-1.06), followed by CKD-EPI21cr with lower bias. The CKD-EPI12cys and JPN eGFRcys also had higher P_{30} and P_{10}, with 90.69 (95% CI, 89.63-91.75) and 91.36% (95% CI, 90.33-92.38) for P_{30}, respectively, and 45.35 (95% CI, 43.53-47.16) for P_{10}, respectively. CKD-EPI21cr and CKD-EPI21cr-cys were next with similarly high P_{30} and P_{10}. Root mean square error was lower for CKD-EPI12cys, JPN eGFRcys, CKD-EPI21cr-cys, CKD-EPI21cr, and JPN eGFRcr in that order. The correlation coefficients in descending order were CKD-EPI12cys: 0.61, CKD-EPI21cr-cys: 0.61, JPN eGFRcys: 0.59, CKD-EPI21cr: 0.50, and JPN eGFRcr: 0.39. The relationship between the mean values of eGFR and mGFR and the difference (Bland-Altman plot) is shown in Figure 1. CKD-EPI21cr, CKD-EPI12cys,

TABLE 1.

Performance of each equation

Equation estimating GFR	Absolute bias, mL/min/1.73 m², mean (95% CI)	Relative bias, %, mean (95% CI)	P_{30}, % (95% CI)	P_{10}, % (95% CI)	RMSE, mL/min/1.73 m²
CKD-EPI12cys	1.76 (0.67 to 2.87)	3.48 (2.17 to 4.80)	90.69 (89.63 to 91.75)	45.35 (43.53 to 47.16)	15.57
CKD-EPI21cr	8.75 (7.61 to 9.90)	7.88 (6.67 to 9.10)	83.11 (81.75 to 84.48)	37.90 (36.13 to 39.67)	18.20
CKD-EPI21cr-cys	10.10 (9.04 to 11.15)	13.11 (11.77 to 14.45)	83.51 (82.16 to 84.86)	37.23 (35.47 to 39.00)	17.83
JPN eGFRcr	12.75 (11.30 to 14.21)	–12.44 (–14.07 to –10.80)	73.94 (72.34 to 75.54)	24.73 (23.16 to 26.31)	23.99
JPN eGFRcys	3.24 (2.80 to 3.70)	–2.35 (–3.63 to –1.06)	91.36 (90.33 to 92.38)	45.35 (43.53 to 47.16)	16.39

CI, confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration; CKD-EPI12cys, CKD-EPI2012 from cystatin C; CKD-EPI21cr, CKD-EPI2021 from creatinine; eGFR, estimated glomerular filtration rate; $eGFR_{cys}$, cystatin C–based eGFR; $eGFR_{Cr}$, creatinine-based eGFR; JPN, Japanese modified; mGFR, measured GFR; RMSE, root mean square error.

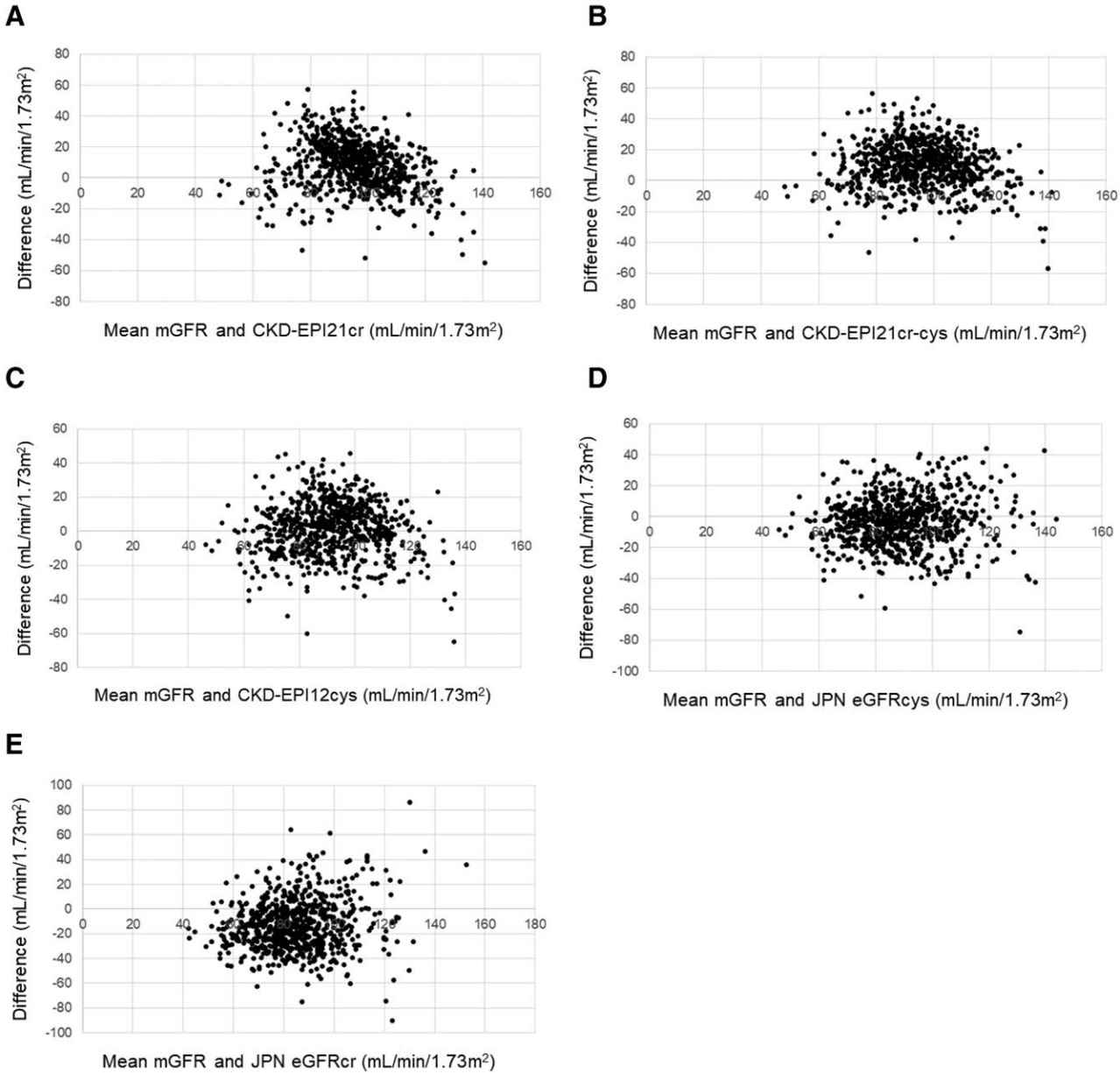

FIGURE 1. Bland-Altman plot between mGFR and (A) CKD-EPI21cr, (B) CKD-EPI21cr-cys, (C) CKF-EPI12cys, (D) JPN eGFRcr, and (E) JPN eGFRcys. CKD-EPI, chronic kidney disease epidemiology collaboration; CKD-EPI12cys, CKD-EPI2012 from cystatin C; CKD-EPI21cr, CKD-EPI2021 from creatinine; eGFR, estimated glomerular filtration rate; JPN, Japanese modified; mGFR, measured GFR.

TABLE 2.

Proportions of misclassified overestimated potential donors for 2 GFR thresholds

	Equation estimating GFR				
GFR threshold, mL/min/1.73 m²	CKD-EPI12cys	CKD-EPI21cr	CKD-EPI21cr-cys	JPN eGFRcr	JPN eGFRcys
90 mL/min/1.73 m²	20.21 (17.34-23.08)	37.37 (33.91-40.82)	31.52 (28.20-34.84)	6.91 (5.10-8.73)	11.04 (8.80-13.28)
Age-adapted threshold	15.96 (13.34-18.57)	21.94 (18.98-24.90)	20.74 (17.85-23.64)	7.31 (5.45-9.17)	10.24 (8.07-12.41)

Values are percentages with 95% confidence intervals within parentheses.
Misclassified overestimated potential donors mean LKDCs with eGFR compatible with a donor and mGFR not compatible with a donor.
CKD-EPI, chronic kidney disease epidemiology collaboration; CKD-EPI12cys, CKD-EPI2012 from cystatin C; CKD-EPI21cr, CKD-EPI2021 from creatinine; eGFR, estimated glomerular filtration rate; $eGFR_{cys}$, cystatin C–based eGFR; $eGFR_{Cr}$, creatinine-based eGFR; JPN, Japanese modified; LKDC, living kidney donor candidate; mGFR, measured GFR.

TABLE 3.

Proportions of misclassified underestimated potential donors for 2 GFR thresholds

	Equation estimating GFR				
GFR threshold, mL/min/1.73 m²	CKD-EPI12cys	CKD-EPI21cr	CKD-EPI21cr-cys	JPN eGFRcr	JPN eGFRcys
90 mL/min/1.73 m²	9.97 (7.83-12.12)	3.86 (2.48-5.23)	3.19 (1.94-4.45)	33.38 (30.01-36.75)	17.29 (14.58-19.99)
Age-adapted threshold	9.71 (7.59-11.82)	3.86 (2.48-5.23)	3.19 (1.94-4.45)	40.69 (37.18-44.20)	19.15 (16.34-21.96)

Values are percentages with 95% confidence intervals within parentheses.
Misclassified underestimated potential donors mean LKDCs with eGFR not compatible with a donor and mGFR compatible with a donor.
CKD-EPI, chronic kidney disease epidemiology collaboration; CKD-EPI12cys, CKD-EPI2012 from cystatin C; CKD-EPI21cr, CKD-EPI2021 from creatinine; eGFR, estimated glomerular filtration rate; $eGFR_{cys}$, cystatin C–based eGFR; $eGFR_{Cr}$, creatinine-based eGFR; JPN, Japanese modified; LKDC, living kidney donor candidate; mGFR, measured GFR.

TABLE 4.

Simulation of the numbers of eligible donors in GFR of 90 mL/min/1.73 m² thresholds according to the methods of GFR evaluation and interpretation

			Misclassified			
Equation estimating GFR	Eligible, n (%)	Difference, n (%)	Overestimation, n (%)	Mean difference, mL/min/1.73 m²	Underestimation, n (%)	Mean difference, mL/min/1.73 m²
mGFR	370 (49.20)	0	0	0	0	0
CKD-EPI12cys	447 (59.44)	77 (10.24)	152 (20.21)	–18.93	75 (9.97)	17.96
CKD-EPI21cr	622 (82.71)	252 (33.51)	281 (37.37)	–22.08	29 (3.86)	17.26
CKD-EPI21cr-cys	583 (77.53)	213 (28.32)	237 (31.52)	–22.09	24 (3.19)	15.64
JPN eGFRcr	171 (22.74)	–199 (26.46)	52 (6.91)	–25.29	251 (33.38)	28.87
JPN eGFRcys	323 (42.95)	–47 (6.25)	83 (11.04)	–17.28	130 (17.29)	20.37

Mean difference: mGFR – eGFR in overestimated or underestimated potential donors.
Misclassified overestimation means LKDCs with eGFR acceptable for kidney donation but mGFR that is not acceptable.
Misclassified underestimation means LKDCs with eGFR not acceptable for kidney donation but mGFR that is acceptable.
CKD-EPI, chronic kidney disease epidemiology collaboration; CKD-EPI12cys, CKD-EPI2012 from cystatin C; CKD-EPI21cr, CKD-EPI2021 from creatinine; eGFR, estimated glomerular filtration rate; $eGFR_{cys}$, cystatin C–based eGFR; $eGFR_{Cr}$, creatinine-based eGFR; JPN, Japanese modified; LKDC, living kidney donor candidate; mGFR, measured GFR.

and CKD-EPI21cr-cys estimated GFR higher, whereas JPN eGFRcr estimated GFR lower.

Impact of eGFR on Donor Selection

Table 2 displays the percentage of misclassified LKDCs into overestimation, where the eGFR meets the threshold criteria, but mGFR does not meet the criteria at 90 mL/min/1.73 m² and age-adapted threshold. At the threshold of 90 mL/min/1.73 m², CKD-EPI21cr had the highest percentage of misclassification into overestimation at 37.37%, whereas JPN eGFRcr had the lowest percentage of misclassification at 6.91%. At the age-adapted approach, JPN eGFRcr had the lowest percentage of misclassification into overestimation at 7.31%. The other eGFR had >10%, and CKD-EPI21cr had the highest percentage of misclassification into overestimation at 21.94%. Conversely, both at the threshold of 90 mL/min/1.73 m² and the age-adapted approach, CKD-EPI21cr-cys had the lowest percentage of misclassification into underestimation at 3.19% (Table 3). JPN eGFRcr had the highest percentage of misclassification into underestimation at 33.38% and 40.69%, respectively.

Number of Eligible Donors

Differences in eligibility of LKDCs according to the method of GFR evaluation at a threshold of 90 mL/min/1.73 m² are presented in Table 4. The number of eligible donors

TABLE 5.

Simulation of the numbers of eligible donors in age-adapted thresholds according to the methods of GFR evaluation and interpretation

			Misclassified			
Equation estimating GFR	Eligible, n (%)	Difference, n (%)	Overestimation, n (%)	Mean difference, mL/min/1.73 m²	Underestimation, n (%)	Mean difference, mL/min/1.73 m²
mGFR	554 (73.67)	0	0	0	0	0
CKD-EPI12cys	601 (79.92)	47 (6.25)	120 (15.96)	–19.53	73 (9.71)	16.74
CKD-EPI21cr	690 (91.76)	136 (18.09)	165 (21.94)	–26.25	29 (3.86)	18.15
CKD-EPI21cr-cys	686 (91.22)	132 (17.55)	156 (20.74)	–23.94	24 (3.19)	13.57
JPN eGFRcr	303 (40.29)	–251 (33.38)	55 (7.31)	-23.35	306 (40.69)	27.31
JPN eGFRcys	487 (64.76)	-67 (8.91)	77 (10.24)	-17.10	144 (19.15)	18.34

Mean difference: mGFR – eGFR in overestimated or underestimated potential donors.
Misclassified overestimation means LKDCs with eGFR acceptable for kidney donation but mGFR that is not acceptable.
Misclassified underestimation means LKDCs with eGFR not acceptable for kidney donation but mGFR that is acceptable.
CKD-EPI, chronic kidney disease epidemiology collaboration; CKD-EPI12cys, CKD-EPI2012 from cystatin C; CKD-EPI21cr, CKD-EPI2021 from creatinine; eGFR, estimated glomerular filtration rate; $eGFR_{cys}$, cystatin C–based eGFR; $eGFR_{Cr}$, creatinine-based eGFR; JPN, Japanese modified; LKDC, living kidney donor candidate; mGFR, measured GFR.

was lower for the JPN eGFRcr and JPN eGFRcys than for mGFR. The other 3 eGFR equations had a higher number of eligible donors than mGFR. Similarly, when age-adapted normal values were considered, the use of eGFR resulted in fewer eligible donors in JPN eGFRcr and JPN eGFRcys (–251 [33.38%] and –67 [8.91%], respectively) compared with mGFR. All other equations had higher eligible donors (Table 5). However, some of the LKDCs determined to be eligible by eGFR were misclassified. For instance, 601 LKDCs (79.92%) were determined to be eligible by CKD-EPI12cys, differing from mGFR by only 8, whereas 120 LKDCs (15.96%) were misclassified into overestimation with an average of –19.53 mL/min/1.73 m² and 73 LKDCs (9.71%) were misclassified into underestimation with an average of 16.74 mL/min/1.73 m². The mean difference of the misclassified cases was relatively high in each equation.

DISCUSSION

Our study underscores the importance of accurate renal function evaluation in the selection of LKDCs. The novel race-independent CKD-EPI21cr-cys formula shows good performance in the evaluation of renal function, demonstrating a balanced performance. However, the formula is not without its limitations, particularly the risk of misclassification through overestimation, which could deem about 20% of otherwise ineligible donors as suitable in the age-adapted thresholds. In the absolute threshold of 90 mL/min/1.73 m², most eGFR equations showed a higher risk of overestimation for LKDCs, whereas JPN eGFRcr had a relatively low overestimation rate. JPN eGFRcr has a lower GFR but a higher risk that LKDCs with a sufficiently high GFR will be determined ineligible for living kidney donors.

Living donor renal transplantation offers numerous benefits for the recipient, yet it poses risks for donors, including the potential for reduced life expectancy associated with decreased GFR. In the general population, a decrease in GFR has been reported to be associated with a reduction in life expectancy in both men and women.[10] However, living donors typically hail from a healthier segment of the population, suggesting their long-term outcomes may be as good as, if not better than, the general populace.[11-13] In a comparative analysis involving 9750 living kidney donors in the United Kingdom and 19 071 participants from the Health Improvement Network database, living kidney donors had significantly lower mortality rates at 10 y of follow-up.[14] A meta-analysis of mid- and long-term follow-up studies reported no evidence to suggest that donors are at higher risk for all-cause mortality compared with healthy nondonors.[15]

The human body can compensate for the removal of one kidney, restoring GFR to approximately 70% of its initial function, although this comes with the long-term risk of glomerular hyperplasia and hyperfiltration, potentially leading to kidney failure. The relative risk of kidney failure is also thought to be increased in living kidney transplant donors. Muzaale et al[16] reported that the estimated risk of kidney failure 15 y after kidney donation was 30.8 per 10 000 for kidney donors and 3.9 per 10 000 for matched healthy nondonors. Accurate preoperative assessment of renal function is crucial to minimize postdonation kidney failure risk. The KDIGO clinical practice guidelines recommend eGFR from serum creatinine as the initial assessment; they also suggest confirming GFR with more precise methods when necessary.[2] The European renal best practice transplantation guideline recommends that when an accurate assessment of GFR is required or when the accuracy of eGFR is questionable GFR should be measured directly using the exogenous clearance method. We measured Cin in all cases in the evaluation of renal function in potential donors, although there is no evidence to support its usefulness, but other guidelines also recommend it in view of the imprecision of eGFR.

According to the KDIGO guidelines, a GFR of ≥90 mL/min/1.73 m² is considered an acceptable donor indication, whereas a GFR of <60 mL/min/1.73 m² is not; the decision to approve a potential donor with a GFR of 60–89 mL/min/1.73 m² should be based on demographic and health profiles related

to the acceptable risk thresholds of the transplant program.[2] Notably, KDIGO does not categorically reject measurements of GFR of 80 mL/min/1.73 m² (ie, <90 mL/min/1.73 m²). If the lifetime risk estimation of kidney failure, calculated considering multiple parameters/risk factors by Grams et al,[17] is below the transplant center's acceptance threshold, then that GFR level is considered acceptable. In the BTS guideline, the recommended threshold levels differ by sex and age.[3,5] Our institution modifies the criteria for donor eligibility with respect to the donor's age. In our investigation, none of the GFR estimation formulas proved entirely reliable at the 90 mL/min/1.73 m² threshold, with all exhibiting a significant propensity for overestimation, except for JPN eGFR. This misclassification risk underscores the need for cautious interpretation of GFR estimates in donor selection. When the age-adapted threshold was used, the risk of misclassification into overestimation was lower for each GFR estimation formula. We believe this value should be <5% to ensure donor safety, and none of the estimation formulas achieved this threshold. JPN eGFRcr had the highest percentage of misclassification into underestimation. This means that if JPN eGFR is used to determine LKD indications, there is a high risk that people who would normally have good renal function will be determined as not indicated. A combination of several GFR estimation formulas may be effective. Indeed, when the mean of JPN eGFRcr and CKD-EPI21cr-cys was used to determine indications of LKDCs, the risk of misclassification into over- and underestimation was 14.6% and 13.7%, with mean differences at –16.8 and 10.7 mL/min/1.73 m², respectively.

One of the limitations of this study is that it primarily, if not exclusively, focused on LKDCs of Japanese ethnicity. Therefore, the results of this study may not be applicable to non-Japanese ethnic groups. In Korea, the Japanese-GFR equation has been reported to be less biased and more accurate than the CKD-EPI and MDRD study equations.[18] Conversely, it is known that the ethnic coefficients of the MDRD study equation differ between Japanese and Chinese individuals.[19] In addition to possible biases such as differences in GFR measurement methods and creatinine assay calibration, ethnic differences in creatinine production, muscle mass, dietary protein, and tubular secretion of creatinine have been suggested as possible explanations. In the CKD-EPI21cr-cys, the removal of the "race" variable, while innovative, has not been adequately validated in ethnicities other than Caucasian and African American in the general population or in the LKDC cohort; the removal of the "race" variable in 2 ethnicities does not mean that it has been validated for all ethnic groups. Furthermore, GFR equations are often created for patients with CKD and may not apply to healthy people like living kidney donors. In the selection of living kidney donors, it is necessary to prevent misclassification into overestimation for the safety of both donors and recipients. To ensure the safety of both donors and recipients, it is imperative to develop new GFR estimation formulas tailored to the specific characteristics of living kidney donors from various ethnic backgrounds. Further research and refinement in GFR estimation and its clinical interpretation will be vital in enhancing the outcomes for living kidney donors and recipients alike.

This study reconfirms the accuracy and importance of renal function assessment in the selection of LKD. In particular, it suggests that the use of the new CKD-EPI21cr-cys formula allows for a race-independent assessment of kidney function. However, it also became clear that there is a risk of misclassification, especially because of overestimation, and further investigation and improvement are needed to ensure the safety of potential donors. Based on our findings, in the evaluation of LKDCs, the precision of the 5 eGFR equation is not sufficient, and they are not reliable enough to replace nuclear GFR. In the future, the development and application of appropriate GFR estimation formulas for LKDCs from different ethnic backgrounds will be required. Such efforts will be an important step toward better clinical outcomes for both donors and recipients. Our study can serve as a milestone on the path to improving the accuracy of renal function assessment, and we eagerly await further research and advancement in this field.

ACKNOWLEDGMENTS

The authors extend their deepest gratitude to Hidefumi Kishikawa and Katsuhiro Nakagawa from the Hyogo Prefectural Nishinomiya Hospital for their invaluable cooperation in the collection of data. They also thank Shiro Takahara from the Transplantation Center at Kansai Medical Hospital for his significant contributions. Their support was essential to the research, and they are profoundly grateful for their assistance.

REFERENCES

1. Sharma V, Roy R, Piscoran O, et al. Living donor kidney transplantation: let's talk about it. *Clin Med (Lond)*. 2020;20:346–348.
2. Lentine KL, Kasiske BL, Levey AS, et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. *Transplantation*. 2017;101:S1–S109.
3. Andrews PA, Burnapp L. British Transplantation Society/Renal Association UK Guidelines for living donor kidney transplantation 2018: summary of updated guidance. *Transplantation*. 2018;102:e307.
4. Richardson R, Connelly M, Dipchand C, et al; Protocols Working Group of the Canadian Blood Services' Living Donation Advisory Committee. Kidney paired donation protocol for participating donors 2014. *Transplantation*. 2015;99:S1–S88.
5. European Renal Best Practice Transplantation Guideline Development Group. ERBP guideline on the management and evaluation of the kidney donor and recipient. *Nephrol Dial Transplant*. 2013;28(Suppl 2):ii1–i71.
6. Inker LA, Eneanya ND, Coresh J, et al; Chronic Kidney Disease Epidemiology Collaboration. New creatinine- and cystatin C-based equations to estimate GFR without Race. *N Engl J Med*. 2021;385:1737–1749.
7. Kakuta Y, Okumi M, Ichimaru N, et al. Utility of the Japanese GFR estimation equation for evaluating potential donor kidney function. *Clin Exp Nephrol*. 2010;14:63–67.
8. Horio M, Imai E, Yasuda Y, et al; Collaborators Developing the Japanese Equation for Estimated GFR. GFR estimation using standardized serum cystatin C in Japan. *Am J Kidney Dis*. 2013;61:197–203.
9. Inker LA, Schmid CH, Tighiouart H, et al; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–29.
10. Turin TC, Tonelli M, Manns BJ, et al. Chronic kidney disease and life expectancy. *Nephrol Dial Transplant*. 2012;27:3182–3186.
11. Segev DL, Muzaale AD, Caffo BS, et al. Perioperative mortality and long-term survival following live kidney donation. *JAMA*. 2010;303:959–966.
12. Munch P, Christiansen CF, Birn H, et al. Is the risk of cardiovascular disease increased in living kidney donors? A Danish population-based cohort study. *Am J Transplant*. 2021;21:1857–1865.
13. Janki S, Dehghan A, van de Wetering J, et al. Long-term prognosis after kidney donation: a propensity score matched comparison of living donors and non-donors from two population cohorts. *Eur J Epidemiol*. 2020;35:699–707.

14. Krishnan N, Mumford L, Lipkin G, et al. Comparison of medium-term outcomes of living kidney donors with longitudinal healthy control in the United Kingdom. *Transplantation*. 2020;104:e65–e74.
15. O'Keeffe LM, Ramond A, Oliver-Williams C, et al. Mid- and long-term health risks in living kidney donors: a systematic review and meta-analysis. *Ann Intern Med*. 2018;168:276–284.
16. Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. *JAMA*. 2014;311:579–586.
17. Grams ME, Sang T, Levey AS, et al. Kidney-failure risk project for the living kidney-donor candidate. *N Engl J Med*. 2016;374:411–421.
18. Kim BS, Lee YK, Choi HY, et al. Is the new GFR equation using inulin clearance a more accurate method for Asian patients? *Clin Nephrol*. 2015;84:331–338.
19. Rule AD, Teo BW. GFR estimation in Japan and Chine: what accounts for the difference? *Am J Kidney Dis*. 2009;53:932–935.