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【 ORIGINAL ARTICLE 】

The Modified Chronic Kidney Disease Epidemiology Collaboration Equation for the Estimated Glomerular Filtration Rate Is Better Associated with Comorbidities than Other Equations in Living Kidney Donors in Japan

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Abstract:

Objective We studied three types of estimated glomerular filtration rate (eGFR) equations and evaluated which type was strongly associated with comorbidities in living kidney transplantation (LKT) donors.

Methods We compared the Japanese modified eGFR, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration equations (Jm-eGFR, Jm-MDRD, and Jm-CKD-EPI, respectively) for Japanese LKT donors with respect to their relationships with obesity, hypertension, diabetes, cardiovascular disease, and stroke.

Results Of the 8,176 enrolled Japanese LKT donors, the eGFR calculated using Jm-CKD-EPI (eGFR/Jm-CKD-EPI) detected significant differences in 4 of 5 comorbidities between the comorbidity-positive and comorbidity-negative groups, whereas the eGFR calculated using Jm-MDRD (eGFR/Jm-MDRD) and Jm-eGFR (eGFR/Jm-eGFR) detected only 3 and 1 comorbidities, respectively. The area under the receiver operating characteristic curve of Jm-CKD-EPI was larger than those of Jm-eGFR and Jm-MDRD for all five comorbidities.

Conclusion We found that the eGFR/Jm-CKD-EPI correlated better with comorbidities than the eGFR/Jm-eGFR and eGFR/Jm-MDRD in Japanese LKT donors. We recommend using the eGFR/Jm-CKD-EPI for the initial assessment of the renal function in LKT donor candidates when evaluating the presence of associated comorbidities.

Key words: hypertension, diabetes mellitus, elderly, glomerular filtration rate

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Introduction

Different estimated glomerular filtration rate (eGFR) equations are used in epidemiology. The eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (eGFR/CKD- EPI) equation has been reported to be superior to that calculated using the Modification of Diet in Renal Disease (eGFR/MDRD) equation for predicting the GFR and its relationship with cardiovascular events or mortality (1-4) in studies conducted in a large community-dwelling population (>1,000).

Owing to the limited availability of cadaveric donations, approximately 80-90% of all kidney transplantations are living kidney transplantations (LKTs) in Japan (5, 6). Since 2007, the proportion of patients 60-69 and 70-79 years old has increased 2- to 3-fold (6). For expanded-criteria LKT donors, including the elderly, the rate of comorbidities, such as hypertension, diabetes, cardiovascular disease (CVD), and stroke, is increased (7).

The Amsterdam Forum report recommended the use of the GFR measured at the time of the donor examination (8);

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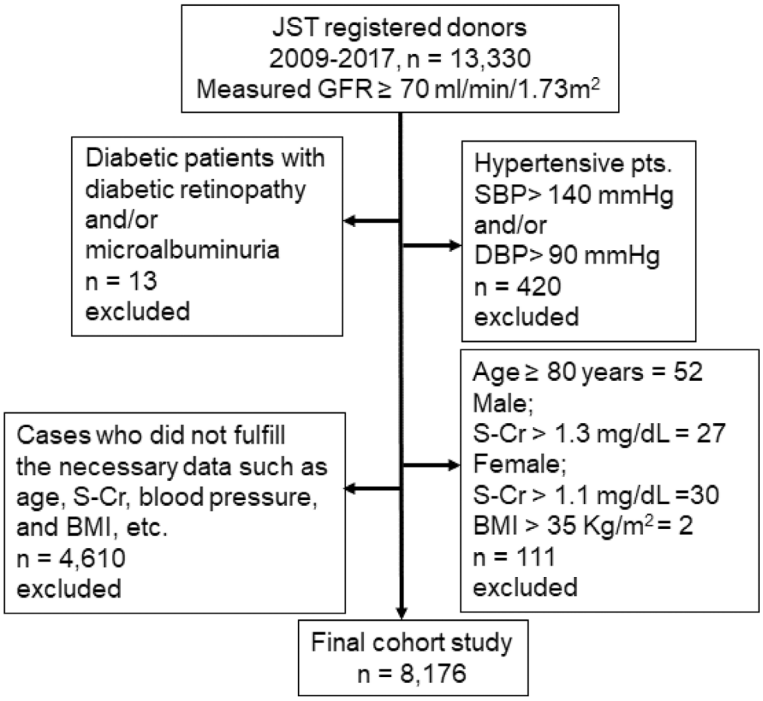

Figure 1. **Flow chart of cohort selection. JST: Japanese Society of Transplantation, Pts: patients, GFR: glomerular filtration, S-Cr: serum creatinine, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure**

however, the eGFR/CKD-EPI and eGFR/MDRD were also used for the initial assessment in clinical settings. The KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors reported the use of the eGFR/CKD-EPI for the initial assessment because of its approximation to the measured GFR (9). In addition, an alternative creatinine-based GFR estimation was deemed acceptable if the accuracy of the eGFR was comparable to that of the measured GFR. The accuracy of the eGFR is important, but the relationship between the eGFR and comorbidities should also be highlighted.

In Japan, the eGFR is computed using the Japanese modified eGFR equation (eGFR/Jm-eGFR) (10) to assess the renal function in clinical settings. The accuracy of the eGFR/Jm-eGFR was significantly better in the range of measuring GFR by inulin clearance (CIn), 0-29 mL/min/1.73 m^2, but not better in the range of CIn, 60-119 mL/min/1.73 m^2 than when using the Japanese modification of CKD-EPI (eGFR/Jm-CKD-EPI) (11). The accuracy of the eGFR calculated using the Japanese modification of MDRD (eGFR/Jm-MDRD) was significantly higher for measuring the GFR using a CIn of <60 mL/min/1.73 m^2, whereas the eGFR/Jm-MDRD underestimated the GFR using a CIn of ≥60 mL/min/1.73 m^2 (12).

To our knowledge, no study has compared the different eGFR equations regarding their relationship with comorbidities in a large LKT donor population. The present study therefore determined which of the three eGFR equations - Jm-eGFR, Jm-MDRD, and Jm-CKD-EPI (10) - has the best association with comorbidities among Japanese LKT donors.

Materials and Methods

The study was approved by the ethics committee of the Japanese Society of Transplantation (JST). We conducted a cross-sectional study using registered data provided by the JST among 13,330 consecutive LKT donors who underwent LKT from 2009 to 2017. Informed consent regarding registration and research was obtained from the registered donors. Pretransplant data, namely age, sex, body mass index (BMI), blood pressure (BP), serum creatinine (SCr), and information on five preclinical comorbidities (obesity, hypertension, diabetes, CVDs, and stroke), were collected. The diagnosis of comorbidities was performed by the doctors in charge based on the patients' medical histories or medication prescriptions.

The JST guidelines (in Japanese) for LKT donors state that the upper age limit is 80 years, but this limit is based on physical age. The JST defines the approved conditions of LKT donors with comorbidities as follows: 1) The upper limit of HbA1c is 6.2% in diabetic cases without medications and 6.5% in diabetic cases with hypoglycemic agents or insulin. Diabetic cases with retinopathy and/or microalbuminuria are not approved as LKT donors. 2) The ideal BMI is ≤30 kg/m^2, and at least BMIs of ≤32 kg/m^2 are necessary. 3) Donor candidates with a history of CVD and stroke must be able to tolerate general anesthesia. CVD includes coronary artery disease and heart failure. Stroke includes cerebral infarction and cerebral hemorrhaging. 4) Hypertension

Table 1. Baseline Data of Donors before Living Kidney Transplantation (n=8,176).

Age (years)	56.2±11.01
Elderly (%)	798 (9.8)
Female (%)	5,266 (64.4)
BMI (kg/m^2)	22.8±3.0
Obesity (%)	143 (1.7)
eGFR/Jm-eGFR (mL/min/1.73 m^2)	79.7±15.5
eGFR/Jm-MDRD (mL/min/1.73 m^2)	83.6±16.6
eGFR/Jm-CKD-EPI (mL/min/1.73 m^2)	80.4±9.6
SBP (mmHg)	119.2±10.8
DBP (mmHg)	71.4±9.3
HT (%)	1,279 (15.6)
DM (%)	334 (4.1)
CVD (%)	155 (1.9)
Stroke (%)	120 (1.5)

Values are presented as mean±standard deviation or n (%). Elderly: age >70 years, BMI: body mass index, obesity: BMI >30 kg/m^2, eGFR: estimated glomerular filtration rate, Jm: Japanese modified, MDRD: Modification of Diet in Renal Disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, SBP: systolic blood pressure, DBP: diastolic blood pressure, HT: hypertension, DM: diabetes, CVD: cardiovascular disease

is defined as a systolic blood pressure (SBP) or diastolic blood pressure (DBP) >140 or 90 mmHg. Patients with SBP/DBP <140/90 mmHg with or without antihypertensive agents are approved as LKT donors.

In this study, we evaluated LKT donors with well-controlled comorbidities within the JST guidelines and excluded very few cases (<1% of 13,330) with extremely deviant data. Specifically, we excluded uncontrolled hypertensive patients with an SBP ≥140 mmHg or DBP ≥90 mmHg, subjects >90 years old, men with an SCr of >1.3 mg/dL and women with an SCr of >1.1 mg/dL, and subjects with a BMI >35 kg/m^2. Donors with insufficient medical data were excluded (Fig. 1). Ultimately, 8,176 participants were enrolled in this study.

The cases with the GFR measured based on the creatinine clearance (CCr) and CIn ≥70 mL/min/1.73 m^2 were approved as LKT donors. Donors with a measured GFR 70-80 and ≥80 mL/min/1.73 m^2 were considered expanded criteria and standard donors, respectively, according to the JST guidelines. However, the measured GFR data are not included in the JST registration.

The formulae for the three eGFR equations are as follows:

Jm-eGFR=$194\times SCr^{-1.094}\times age^{-0.287}\times 0.739$ (for women) (12),

Jm-MDRD=$0.808\times 175\times SCr^{-1.154}\times age^{-0.203}\times 0.742$ (for women) (12),

Jm-CKD-EPI=$0.813\times 141\times \min(SCr/\kappa, 1)^{\alpha}\times \max(SCr/\kappa, 1)^{-1.209}\times 0.993^{age}\times 1.018$ (for women) (12),

where κ is 0.9 for men and 0.7 for women, α is -0.411 for men and -0.329 for women, min is the minimum of SCr/κ or 1, and max is the maximum (SCr/κ, 1) or 1.

Statistical analyses

Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented as percentages. Statistical analyses were performed using the SPSS version 18.0 software program (IBM, Armonk, USA). Continuous variables were compared using Student's t-test. Noncontinuous variables were analyzed using the chi-square test. Correlations were assessed using a Pearson's correlation analysis. Receiver operating characteristic (ROC) curves were drawn between eGFR values calculated using the three equations and comorbidities. For the trend analysis, we used the Jonckheere-Terpstra analysis. Two-sided p values <0.05 were considered statistically significant.

Results

Baseline data are presented in Table 1. We compared the mean eGFR for the three types of equations between the elderly (age >70 years old) and non-elderly groups and between the comorbidity-positive and comorbidity-negative groups (Table 2) and observed significant differences between the elderly and non-elderly groups for all three eGFRs. When comparing mean eGFR/Jm-eGFR, obesity, hypertension, and CVD exhibited significant differences. When comparing the mean eGFR/Jm-MDRD, significant differences were detected only in obesity. When comparing the mean eGFR/Jm-CKD-EPI, obesity, hypertension, diabetes, and CVD exhibited significant differences. No significant differences in the mean eGFR were observed for stroke using each equation.

The positive rates of the 5 comorbidities in the elderly (age >70 years old) and non-elderly groups are shown in Fig. 2. The positive rates for hypertension, diabetes, stroke, and CVD were two to three times higher in the elderly than in the non-elderly group. Chi-square tests for an older age (>70 years old) and comorbidity rates exhibited significant differences (p<0.001).

The correlations between the age and eGFR calculated using the 3 equations were significant (p<0.001). The R^2 of the eGFR/Jm-CKD-EPI (R^2=0.509) was larger than that of the eGFR/Jm-eGFR (R^2=0.150) and eGFR/Jm-MDRD (R^2=0.083).

Fig. 3a shows the ROC analysis between the eGFRs calculated using the three equations and the five comorbidities of obesity, hypertension, diabetes, CVD, and stroke. The ROC curves of the eGFR/Jm-CKD-EPI exhibited a leftward shift compared with those of the eGFR/Jm-eGFR and eGFR/Jm-MDRD in relation to the comorbidities. In particular, regarding the relationship with an older age (>70 years old), the area under the ROC curve (AUROC) for the eGFR/Jm-CKD-EPI was much larger, (0.859) than that for the eGFR/Jm-eGFR (0.674) and eGFR/Jm-MDRD (0.636). Fig. 3b shows results of the ROC analysis between the eGFR calculated using the 3 equations and the 5 comorbidities, excluding an older age (>70 years old), (n=798). The ROC curves

Table 2. Comparisons of the eGFR Calculated Using Three Equations between the Elderly and Non-elderly Groups and between the Comorbidity-positive and Comorbidity-negative Groups.

	eGFR/Jm-eGFR (mL/min/1.73 m^2)			eGFR/Jm-MDRD (mL/min/1.73 m^2)			eGFR/Jm-CKD-EPI (mL/min/1.73 m^2)		
	+	-	p	+	-	p	+	-	p
Elderly	71.8±13.5	80.5±15.5	<0.001	77.0±15.3	84.3±16.6	0.015	71.3±6.7	82.6±9.4	<0.001
Obesity	82.7±17.1	79.6±15.5	0.023	86.2±18.0	83.5±16.5	0.040	83.8±10.9	81.4±9.7	0.023
HT	75.2±14.7	79.7±16.4	0.004	84.3±16.5	79.7±16.4	ns	76.3±8.4	82.4±9.7	<0.001
DM	77.5±14.6	79.8±15.5	ns	82.1±16.2	83.6±16.6	ns	77.4±8.0	81.6±9.8	<0.001
CVD	74.2±12.9	79.8±15.2	0.032	78.3±14.2	83.7±16.6	ns	75.8±8.0	81.6±9.7	<0.001
Stroke	74.5±14.5	79.7±15.5	ns	78.9±16.1	83.6±16.5	ns	75.7±8.5	81.5±9.7	ns

eGFR: estimated glomerular filtration rate, Jm: Japanese modified, MDRD: Modification of Diet in Renal Disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, elderly: age >70 years, obesity: body mass index >30 kg/m^2, HT: hypertension, DM: diabetes, CVD: cardiovascular disease

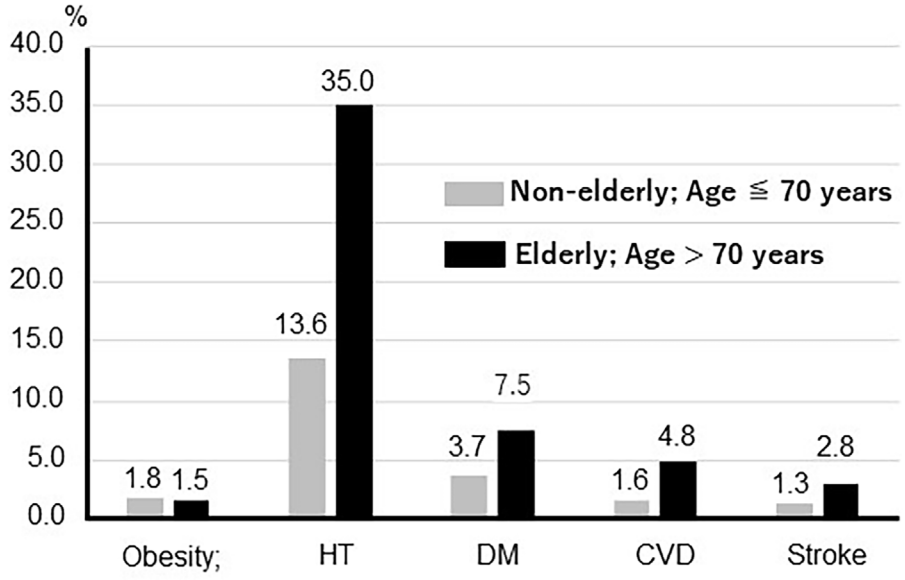

Figure 2. Comorbidity rates in the non-elderly and elderly groups. Excluding obesity (body mass index >30 kg/m^2), the rates of comorbidities in the elderly group (age >70 years old) were 2-3 times higher than those in the non-elderly (age ≤70 years old) group. HT: hypertension, DM: diabetes, CVD: cardiovascular disease

of the eGFR/Jm-CKD-EPI presented a leftward shift compared with those of the eGFR/Jm-eGFR and eGFR/Jm-MDRD in relation to the comorbidities.

The comorbidity rates, namely <70 mL/min/1.73 m^2, 70-80 mL/min/1.73 m^2, and ≥80 mL/min/1.73 m^2, in the 3 eGFR groups are presented in Table 3. All five comorbidities showed significant differences only in the group with eGFR/Jm-CKD-EPI, and the comorbidity rates in the group with eGFR/Jm-CKD-EPI <70 mL/min/1.73 m^2 were higher than those in the group with eGFR ≥70 mL/min/1.73 m^2.

Discussion

Of the three eGFRs, the eGFR/Jm-CKD-EPI correlated most sensitively with the comorbidities. The eGFR/Jm-CKD-EPI, eGFR/Jm-eGFR, and eGFR/Jm-MDRD detected significant differences in four, three, and one of the five comorbidities, respectively (Table 2). In the ROC analyses (Fig. 3), the eGFR/Jm-CKD-EPI was superior in terms of the relationship between comorbidities. A trend analysis (Table 3) revealed the superiority of the eGFR/Jm-CKD-EPI in the decline of the eGFR (Fig. 3).

During donor candidate evaluation before transplantation, the eGFR/CKD-EPI can be used for the initial assessment. Extra care should be provided to patients who have received donations from donors with a low eGFR/CKD-EPI (<70 mL/min/1.73 m^2), which is most strongly associated with the five comorbidities and an older age (Table 3). Compared to donations from healthy living donors, those from living donors with medical conditions (so-called expanded criteria donors) exhibited a high incidence of overall and death-censored graft loss according to multivariable Cox proportional hazards analyses (hazard ratios=2.16 and 3.25, p= 0.015 and 0.004, respectively) (7).

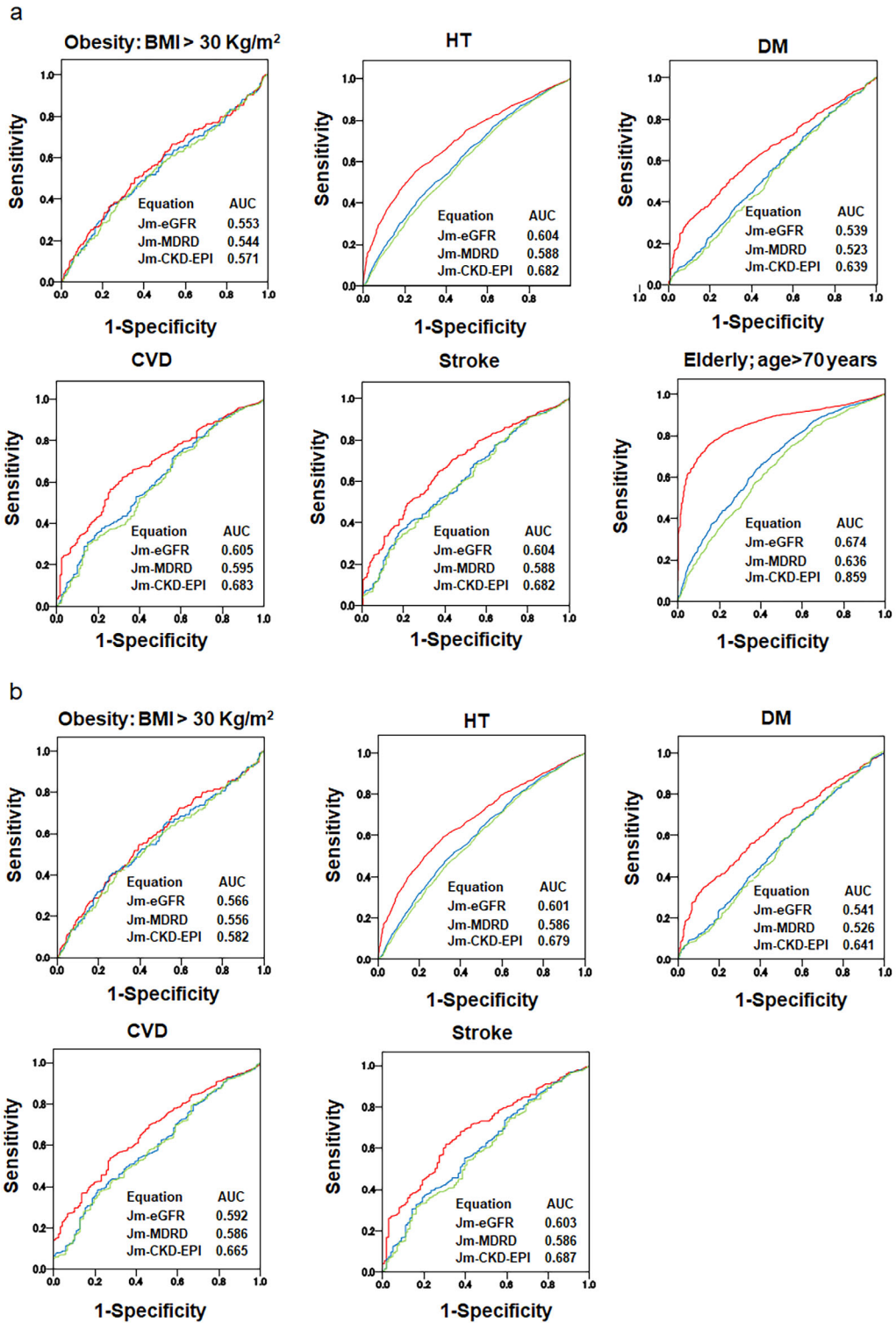

Figure 3. **a: The AUROC using the ROC analysis for the relationship with comorbidities calculated by the eGFR using the three equations of Jm-eGFR, Jm-MDRD, and Jm-CKD-EPI. The AUROC is shown graphically for each ROC analysis between the eGFR and comorbidities. n=8,176. b: The AUROC using the ROC analysis for the relationship with comorbidities calculated by the eGFR using the three equations of Jm-eGFR, Jm-MDRD, and Jm-CKD-EPI, excluding the elderly (age >70 years old). n=7,378. AUROC: area under the receiver operating characteristics curve, ROC: receiver operating characteristics, AUC: area under the curve, BMI: body mass index, eGFR: estimated glomerular filtration rate, HT: hypertension, DM: diabetes, CVD: cardiovascular disease, Jm: Japanese modified, MDRD: Modification of Diet in Renal Disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration. The red line is Jm-CKD-EPI, the blue line is Jm-eGFR, and the green line is Jm-MDRD.**

Table 3. The Comorbidity Rates in Three eGFR Groups <70, 70-80, ≥80 mL/min/1.73m^2 calculated by Each eGFR Equation.

	eGFR/Jm-eGFR (mL/min/1.73m^2)				eGFR/Jm-MDRD (mL/min/1.73m^2)				eGFR/Jm-CKD-EPI (mL/min/1.73 m^2)			
	<70	70-80	≥80		<70	70-80	≥80		<70	70-80	≥80	
n	2,282	2,309	3,585	p	1,665	2,060	4,451	p	911	2,665	4,600	p
Elderly(%)	17.3	9.0	5.4	<0.001	17.4	10.4	6.6	<0.001	33.8	16.9	0.9	<0.001
Obesity(%)	1.6	1.4	2.1	ns	1.6	2.9	2.0	ns	1.8	1.2	2.1	0.023
HT (%)	22.0	16.5	11.0	<0.001	22.8	16.3	12.7	<0.001	28.2	22.5	9.2	<0.001
DM (%)	5.0	3.9	3.7	0.021	5.1	4.0	3.8	0.036	6.0	5.9	2.7	<0.001
CVD (%)	2.8	2.1	1.2	<0.001	3.0	1.9	1.5	<0.001	4.0	2.6	1.1	<0.001
Stroke (%)	2.3	1.2	1.1	0.001	2.3	1.5	1.2	0.003	2.8	2.4	0.7	<0.001

p values were evaluated by Jonckheere-Terpstra analysis.

eGFR/Jm-eGFR: estimated glomerular filtration rate, JM: Japanese modified, MDRD: Modification of Diet in Renal Disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, Elderly: age >70 years, Obesity: body mass index >30 kg/m^2, HT: hypertension, DM: diabetes, CVD, cardiovascular disease

In cross-sectional studies, a lower eGFR/CKD-EPI showed a better association with the prevalence of comorbidities than eGFR/MDRD in Caucasian community-dwelling populations. Tarantini et al. (4) reported that in patients with CVD, the prevalence of CVD was higher when evaluating the eGFR/CKD-EPI than when evaluating the eGFR/MDRD in the low eGFR group. Juutilainen et al. (13) evaluated the rates of comorbidities, namely hypertension, obesity, diabetes, and CVD, in patients with CKD and observed a significantly higher prevalence of patients with comorbidities when the evaluation was performed using the eGFR/CKD-EPI than when it was performed using the eGFR/MDRD.

We confirmed the accuracy of the eGFR/Jm-CKD-EPI in the literature. Rule et al. (14) reported that the CKD-EPI equation was more accurate than MDRD in low-risk populations, including pre-donation and post-donation kidney donors. Murata et al. (15) reported that the creatinine-based eGFR/CKD-EPI demonstrated less bias than the eGFR/MDRD in potential LKT donors (−8% vs. −18%). Burballa et al. (16) and Gaillard et al. (17) compared the values of the creatinine-based eGFR/CKD-EPI, eGFR/MDRD, and mGFR with isotopes in preoperative LKT donors and concluded that the eGFR/CKD-EPI correlated better with mGFR than did the eGFR/MDRD. Horio et al. (18) compared the accuracy of the eGFR/Jm-CKD-EPI and eGFR/Jm-MDRD with the measured inulin GFR in a health checkup population in Japan. In the rage of measured inulin GFR ≥60 mL/min/1.73 m^2, the biases (mGFR-eGFR) were 7.3±20.6 mL/min/1.73 m^2 in the eGFR/Jm-CKD-EPI and 7.8 ±22.2 mL/min/1.73 m^2 in the eGFR/Jm-MDRD, respectively (p<0.001). Horio et al. (19) evaluated the accuracy of the eGFR/Jm-eGFR in potential LKT donors in Japan who received the inulin clearance test and observed a bias (mGFR-eGFR) of 18.3±16.4 mL/min/1.73 m^2. Thus, the eGFR/Jm-eGFR underestimated the true GFR of LKT donors. Based on the two studies of Horio et al. (18, 19), the eGFR/Jm-CKD-EPI appears accurate for comparing measured inulin GFR values.

We explored why the eGFR/Jm-CKD-EPI was superior regarding its relationship with the five evaluated comorbidities, as the reasons have not been examined in-depth in previous reports. The comorbidity rates were 2 to 3 times higher in the elderly group (age >70 years old) than in the non-elderly group (age ≤70 years old) among the LKT donors (Fig. 3). An ROC analysis revealed that the eGFR/Jm-CKD-EPI was better associated with an older age (>70 years old) compared to the eGFR/Jm-eGFR and eGFR/Jm-MDRD (Fig. 3a). We thus believe that the equation characteristic of age sensitivity is responsible for the superiority of the eGFR/Jm-CKD-EPI.

Ji et al. studied the relationship between the eGFR and preclinical target organ damage in hypertension using an ROC analysis and reported that the eGFR/Chinese CKD-EPI equation was better associated with hypertensive complications than the eGFR/Chinese and Asian- modified MDRD equations (20). The eGFR/CKD-EPI was better associated than the eGFR/MDRD with intra-media thickness, ankle-brachial index, left ventricular mass index, urine albumin-to-creatinine ratio, and aortic pulse wave velocity. In our study, discounting elderly cases, the eGFR/CKD-EPI was better associated with comorbidities in LKT donors than the eGFR/Jm-eGFR and eGFR/Jm-MDRD (Fig. 3b). Thus, the eGFR/CKD-EPI might be sensitive for hypertensive or atherosclerotic complications, excluding the older age factor. The eGFR/Jm-CKD-EPI is recommended for use in risk evaluations, not only for renal damage but also systemic organ damage, reflecting hypertensive complications in LKT donors.

The eGFR/CKD-EPI has been reported to be superior to the eGFR/MDRD in the prediction of CVD events or mortality in Caucasian participants (1-3). In Chinese participants, the eGFR/CKD-EPI was a better predictor of stroke recurrence and death than the eGFR/MDRD (21). Consistently, Matsushita et al. (22) reported that the eGFR/Jm-CKD-EPI was a better predictor of the risk of all-cause and

cardiovascular mortalities than the eGFR/Jm-MDRD in the range of the eGFR ≥60 mL/min/1.73 m^2 in Japanese participants. Terawaki et al. (3) used an ROC analysis to compare the predictive values for CVD and stroke between the eGFR/Jm-CKD-EPI and eGFR/Jm-MDRD and reported that the AUROCs for CVD events in the eGFR/Jm-CKD-EPI and eGFR/Jm-eGFR were 0.596 and 0.562, respectively. The eGFR/CKD-EPI was more closely associated with CVD incidence in 241,159 Japanese participants (mean age, 64 years old) who were undergoing a general health checkup. Ohsawa et al. (23) reported a better prediction for all-cause mortality, myocardial infarction, and stroke with the eGFR/Jm-CKD-EPI than with the eGFR/Jm-MDRD in a health checkup cohort. Thus, the eGFR/CKD-EPI is superior for predicting CVD events and mortality in community-dwelling populations. We should carefully follow-up donors with a low eGFR/CKD-EPI after transplantation.

Several limitations associated with the present study warrant mention. The registry data had no data on the measured GFR, so we could not directly compare the accuracy of the three eGFR equations. We unfortunately had to exclude many cases with missing data from the analysis. These limitations might have resulted in the data being misclassified; however, our study has some important insights derived from its involvement of a large cohort of LKT donors (> 8,000 cases).

Conclusion

The eGFR/Jm-CKD-EPI was better associated with comorbidities, including obesity, hypertension, diabetes, CVD, and stroke, than the eGFR/Jm-eGFR and eGFR/Jm-MDRD in low-risk populations, such as Japanese LKT donors. For the initial assessment of the renal function of LKT donor candidates, the eGFR/Jm-CKD-EPI is recommended, particularly for expanded criteria donors with comorbidities.

The authors state that they have no Conflict of Interest (COI).

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