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Comparison of glomerular filtration rate estimating formulas among Japanese adults without kidney disease

Ryosuke Fujii [a,b,*], Cristian Pattaro [a], Yoshiki Tsuboi [b], Yuya Ishihara [b], Roberto Melotti [a], Hiroya Yamada [c], Yoshitaka Ando [d], Hiroaki Ishikawa [d], Koji Ohashi [d], Shuji Hashimoto [c], Nobuyuki Hamajima [e], Giulia Barbieri [a,f], Dariush Ghasemi-Semeskandeh [a,g], Koji Suzuki [b]

[a] Institute for Biomedicine (affiliated to the University of Lübeck), Eurac Research, via Alessandro Volta 21, 39100 Bolzano/Bozen, Italy
[b] Department of Preventive Medical Sciences, Fujita Health University School of Medical Sciences, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake 470-1192 Japan
[c] Department of Hygiene, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake 470-1192 Japan
[d] Department of Biomedical and Analytical Sciences, Fujita Health University School of Medical Science, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake 470-1192 Japan
[e] Department of Healthcare Administration, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550 Japan
[f] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Piazzale Ludovico Antonio Scuro 10, 37124 Verona, Italy
[g] Department of Human Genetics, Leiden University Medical Center, Einthovenweg 20, 2333 ZC Leiden, the Netherlands

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ABSTRACT

Background: Previous studies have proposed different formulas of estimating glomerular filtration rate (eGFR) among clinical patients. The comprehensive comparison of eGFR formulas is not well established in a Japanese population. We compared eGFR values and chronic kidney disease (CKD) classification of nine different eGFR in a Japanese general population sample.

Methods: We analyzed 469 Japanese community-dwelling adults (184 men) without any self-reported kidney disease. GFR estimated using the 4- and 6-parameter Modification of Diet in Renal Disease (MDRD) formulas (MDRD4 and MDRD6); the CKD-EPI formulas based on creatinine with (CKD-EPI-2009) and without race coefficient (CKD-EPI-2021), on cystatin C (CKD-EPI-Cys), on both (CKD-EPI-CreCys); the Japanese creatinine-based formula (JPN-Cre), cystatin C-based formula (JPN-Cys), and modified CKD-EPI formula (JPN-CKD-EPI). CKD stages were defined by KDIGO guidelines (eGFR $<$ 60 ml/min/1.73 m^2).

Results: $eGFR_{JPN\text{-}Cre}$ (mean = 71.2; SD = 14.3) were much lower than $eGFR_{CKD\text{-}EPI\text{-}2021}$ (mean = 94.2; SD = 12.7), while $eGFR_{JPN\text{-}Cys}$ (mean = 102.8; SD = 24.2) was comparable to the MDRD and CKD-EPI formulas. The difference between $eGFR_{CKD\text{-}EPI\text{-}2021}$ and $eGFR_{JPN\text{-}Cre}$ showed a V-shaped distribution across eGFR levels, indicating complex errors between these formulas. We observed very low agreement in CKD classification between $eGFR_{JPN\text{-}Cre}$ and the $eGFR_{CKD\text{-}EPI\text{-}2021}$ (kappa = 0.13; 95% confidence interval: 0.06, 0.23).

Conclusions: JPN-Cre was substantially different from the CKD-EPI formula without race term (CKD-EPI-2021), which means that it is impossible to recalibrate those with a simple coefficient. Although a comparison with measured GFR should be necessary, choice of the estimation method needs caution in clinical decision-making and academic research.

1. Introduction

Glomerular filtration rate (GFR) is the key indicator to reflect filtration function in the kidney and to diagnose chronic kidney disease (CKD) in clinical settings [1]. GFR can be measured invasively using exogenous markers, with time-consuming procedures and substantial variability across methods [2]. For decision-making in clinical settings, estimated GFR (eGFR) is reported based on endogenous biomarkers such as serum creatinine and cystatin C. Many approaches for GFR estimation have been developed. Levey AS et al introduced the Modification of Diet in Renal Disease (MDRD) formula in 1999, that was improved in 2006 [3,4]. Later on, the Chronic Kidney Disease Epidemiology Collaboration

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

* Corresponding author at: Institute for Biomedicine, Eurac Research (affiliated to the University of Lübeck), via Alessandro Volta 21, 39100 Bolzano/Bozen, Italy.
E-mail address: rfujii@eurac.edu (R. Fujii).

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(CKD-EPI) equations were introduced [5,6], and soon became the gold-standard in both population-based and clinical studies [7–11]. The Task Force from the National Kidney Foundation and American Society of Nephrology has recommended the implementation of a novel equation (CKD-EPI-2021) to remove the race coefficient and promote equity across ancestries [12]. This formula could be expected to increase the generalizability of the eGFR estimates across different populations.

In Japan, specific coefficients were applied for the eGFR formulas developed in US populations to adjust for biological differences [13,14]. For example, a Japanese coefficient of 0.813 was adopted to the formula of CKD-EPI-2009 [15]. At the same time, a novel Japanese-specific formula based on serum creatinine was developed in 2009 and has been implemented in daily clinical practice in Japan [16]. In China, a different coefficient of 1.23 was introduced for the MDRD formula, which was inverse of the Japanese coefficient [17]. A previous commentary and recent review paper pointed out that this difference for adjustments across Asian populations may be due to differences in the exogenous markers used for objective GFR quantification and on creatinine measurement methods rather than biological aspects [18,19]. In addition, population-specific coefficients are never validated in different populations but just within the country where they were developed, making international comparison extremely difficult.

It may be meaningful to assess the extent to which various eGFR formulas differ in a general population. The main purpose of this work was to compare eGFR levels and CKD categories obtained by nine separate formulas in a Japanese general population setting.

2. Materials and methods

2.1. Study participants

We included in this study 526 participants in the Yakumo study 2011, a population-based study based on the health check-up annual program. Participants were recruited from the community-dwelling adults of Yakumo, a countryside town in the northernmost prefecture of Japan. They must be above 40 years old at the health check-up. Before the health check-up, participants filled out a self-administered questionnaire on their demographic characteristics, lifestyle, and medical history (including a clinical history of hypertension, diabetes, and kidney disease). With regard to tobacco smoking and alcohol drinking, participants answered the questions "Have you ever smoked?" and "Have you ever drunk alcohol?" with three options: "Current", "Ever", and "Never". For medical history, the standard question specific to each disease was "Have you ever had this disease?" with four options: "Yes (without treatment)", "Yes (treated)", "Yes (under treatment)", and "No". At the study site, participants underwent anthropometric measurements and blood drawing. We excluded 57 participants from our analyses for the following reasons: informed consent not provided (n = 12); preexisting history of kidney disease (n = 33); and missing values in clinical and demographic traits (n = 12). This left 469 participants (184 men, 285 women) for this study. The study was approved by the Ethics Committee of Fujita Health University (HM 19–061). All participants considered in this analysis signed written informed consent.

2.2. Measurement of serum creatinine and cystatin C

Morning fasting serum samples (skipping breakfast, basically more than eight hours) were separated from blood cells by centrifugation within one hour of collection during the health examination. The samples were stored at −80 °C until biochemical measurement. Serum cystatin C levels were measured using a latex agglutination turbidimetric method (Cystatin C-latex Seiken; Denka Co., Ltd., Tokyo, Japan) using auto-analyzers (BiOLis 24i; Tokyo Boeki Medisys Inc., Tokyo, Jap. Serum creatinine levels were measured using an enzymatic method. Serum creatinine and other biochemical analyses were performed using auto-analyzers (JCM-BM9130; Nihon Denshi Co., Ltd., Tokyo, Japan) in the laboratory at Yakumo General Hospital.

2.3. Formulas for eGFR and CKD classification

We estimated GFR using nine different formulas as summarized in Supplementary Table 1: 1. The 2009 CKD-EPI equation based on serum creatinine (CKD-EPI-2009) [5]; 2. the 2021 CKD-EPI equation based on serum creatinine without race coefficient (CKD-EPI-2021) [12]; 3. the CKD-EPI equation based on serum cystatin C (CKD-EPI-Cys) [6]; 4. the CKD-EPI equation based on both serum creatinine and cystatin C (CKD-EPI-CreCys) [6]; 5. the Japanese-specific formula based on serum creatinine (JPN-Cre), which is commonly used in reporting laboratory testing results in Japan [16]; 6. the modified CKD-EPI-2009 formula adapted to the Japanese population (JPN-CKD-EPI) [15]; 7. the Japanese formula based on serum cystatin C (JPN-Cys) [20]; 8. the 4-parameter MDRD study equation (MDRD4) [3]; 9. and the 6-parameters MDRD study equation (MDRD6) [4]. We calculated the eGFR for the CKD-EPI and MDRD formulas using the R package "*nephro*" (ver.1.0.0) [21]; otherwise calculated it using our own codes. CKD was defined as eGFR < 60 ml/min/1.73 m^2 with each formula.

2.4. Statistical analysis

To better characterize eGFR distributions we used ridgeline plots rather than classical boxplots. The Bland-Altman plot was used to assess systematic differences of the eGFR levels against the measurements of the $eGFR_{JPN\text{-}Cre}$ as a reference formula [22]. Unweighted and weighted kappa statistics were used to assess agreement between the corresponding CKD classifications [23], in terms of presence/absence (eGFR < 60, ≥ 60) and in terms of CKD ordered classes (eGFR < 45, 45–59, 60–89, and ≥ 90). The linear weight was applied in our analysis. We performed these analyses using the R package "*irr*" version 0.84.1 (https://CRAN.R-project.org/package=irr). To calculate bootstrap-based confidence intervals for kappa statistics, we also used the R package "*boot*" (https://CRAN.R-project.org/package=boot). All statistical analyses were performed using the R software package version 4.0.0 (https://www.r-project.org).

3. Results

Study participants' characteristics are summarized in Table 1. Of 469 participants, 285 (60.8 %) were women and the overall mean age was 65.7 (standard deviation, SD = 10.0). History of diabetes or hypertension was reported by 44 (9.4 %) and 177 (37.8 %) participants, respectively.

3.1. Distribution of eGFR using different formulas

Fig. 1 shows distributions of eGFR calculated with the different formulas. $eGFR_{JPN\text{-}Cre}$ had the lowest mean level among all formulas (mean = 71.2; SD = 14.3), while the highest mean level was observed

Table 1
Clinical characteristics of study participants.

Variables	units	Men (n = 184)	Women (n = 285)
Age	years	66.0 (10.0)	65.6 (10.0)
Serum creatinine	mg/dL	0.86 (0.19)	0.66 (0.12)
Blood urea nitrogen	mg/dL	15.9 (4.5)	15.1 (4.1)
Serum cystatin C	mg/L	0.76 (0.17)	0.71 (0.16)
Type 2 diabetes	n, %	21 (11.4 %)	23 (8.1 %)
Hypertension	n, %	67 (36.4 %)	110 (38.6 %)
Habitual drinking	n, %	123 (66.8 %)	73 (25.6 %)
Tobacco smoking	n, %	29 (15.8 %)	22 (7.7 %)

Values are reported as mean (SD) for quantitative variables and as n (%) for categorical variables. Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; urea nitrogen in mg/dL to mmol/L, ×0.357.

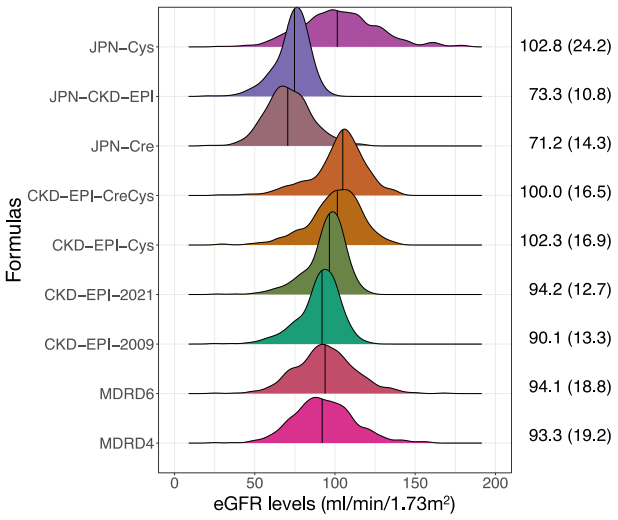

Fig. 1. Distribution of eGFR according to the different formulas. The figures on right of each plot represent mean (standard deviation) of the corresponding eGFR levels. The vertical lines in the plot indicate median of the corresponding eGFR levels.

for $eGFR_{JPN\text{-}Cys}$ (mean = 102.8; SD = 24.2). Compared with $eGFR_{CKD\text{-}EPI\text{-}2021}$ (mean = 94.2; SD = 12.7), $eGFR_{JPN\text{-}Cre}$ was, on average, 20 ml/min/1.73 m^2 lower. A similar difference was observed when comparing $eGFR_{JPN\text{-}Cre}$ against other formulas developed in the US population. Of nine formulas, only $eGFR_{JPN\text{-}CKD\text{-}EPI\text{-}2009}$ (mean = 73.3; SD = 10.8) was comparable to $eGFR_{JPN\text{-}Cre}$. After stratification by demographic and clinical factors (sex, age group, diabetes, and hypertension), we compared eGFR derived from nine different formulas (Supplementary Table 2). The deviation of eGFR between each formula was greater in younger and healthier populations without a clinical history of diabetes or hypertension.

3.2. Systematic difference of eGFR compared with $eGFR_{JPN\text{-}Cre}$

The Bland-and-Altman plots in Fig. 2 show the patterns of the differences of all formulas against the JPN-Cre. On average, $eGFR_{JPN\text{-}Cre}$ was lower compared to all other formulas by 20–30 ml/min/1.73 m^2, except for $eGFR_{JPN\text{-}CKD\text{-}EPI}$. For $eGFR_{JPN\text{-}CKD\text{-}EPI}$, the plot shows perfect agreement with $eGFR_{JPN\text{-}Cre}$ for eGFR levels < 60; there is little difference between 60 and 80, and much higher than $eGFR_{JPN\text{-}Cre}$ for values above 80; thus the two formulas perform similarly for CKD classification, but quite differently for CKD staging, and by deduction for association studies on eGFR. For $eGFR_{JPN\text{-}Cys}$, $eGFR_{MDRD4}$, and $eGFR_{MDRD6}$, the difference from $eGFR_{JPN\text{-}Cre}$ monotonously increased as mean eGFR levels increase, indicating larger differences in healthier individuals. For $eGFR_{CKD\text{-}EPI\text{-}Cys}$, on average, the eGFR levels were lower in the JPN-Cre; furthermore, if the few individuals at the tails are excluded (at extremely low and high eGFRs), for the remaining points we observed a cloud of uncorrelated points, i.e. agreement should be extremely poor. For the three remaining formulas ($eGFR_{CKD\text{-}EPI\text{-}2009}$, $eGFR_{CKD\text{-}EPI\text{-}2021}$, and $eGFR_{CKD\text{-}EPI\text{-}CreCys}$), the eGFR levels were also larger than the JPN-Cre at most eGFR levels. However, unlike the other formulas, the difference with $eGFR_{JPN\text{-}Cre}$ showed the non-linear trend of a V-shape. The slope was negative for eGFR levels < 80, while it reverted to positive for eGFR levels greater than 80.

3.3. Differences of CKD classification and eGFR categories

Fig. 3 shows the agreement of CKD classification between all pairs of nine formulas. Overall, CKD classification of JPN-Cre had less agreement with most other formula pairwise comparisons (kappa: 0.13 to 0.23) except for the high concordance with JPN-CKD-EPI (kappa: 0.65; 95%

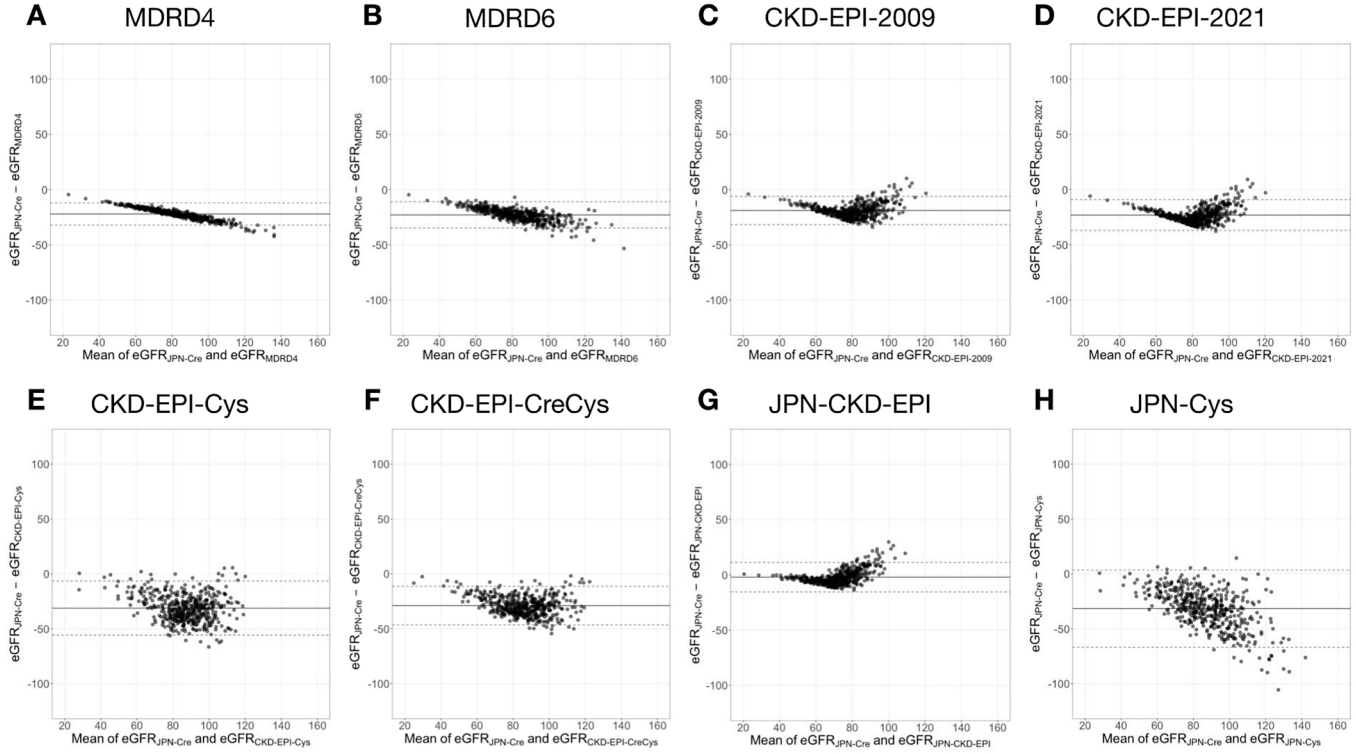

Fig. 2. Bland-Altman plot for the difference of $eGFR_{JPN\text{-}Cre}$ with eGFR from other formulas. A: MDRD4, B: MDRD6, C: CKD-EPI-2009, D: CKD-EPI-2021, E: CKD-EPI-Cys, F: CKD-EPI-CreCys, G: JPN-CKD-EPI, H: JPN-Cys. Mean (X-axis) indicates the mean value of $eGFR_{JPN\text{-}Cre}$ and each eGFR. Difference (Y-axis) indicates the difference between $eGFR_{JPN\text{-}Cre}$ and each eGFR. Black solid line shows the mean difference between two eGFR values. Red dashed lines show 1-SD difference in both directions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

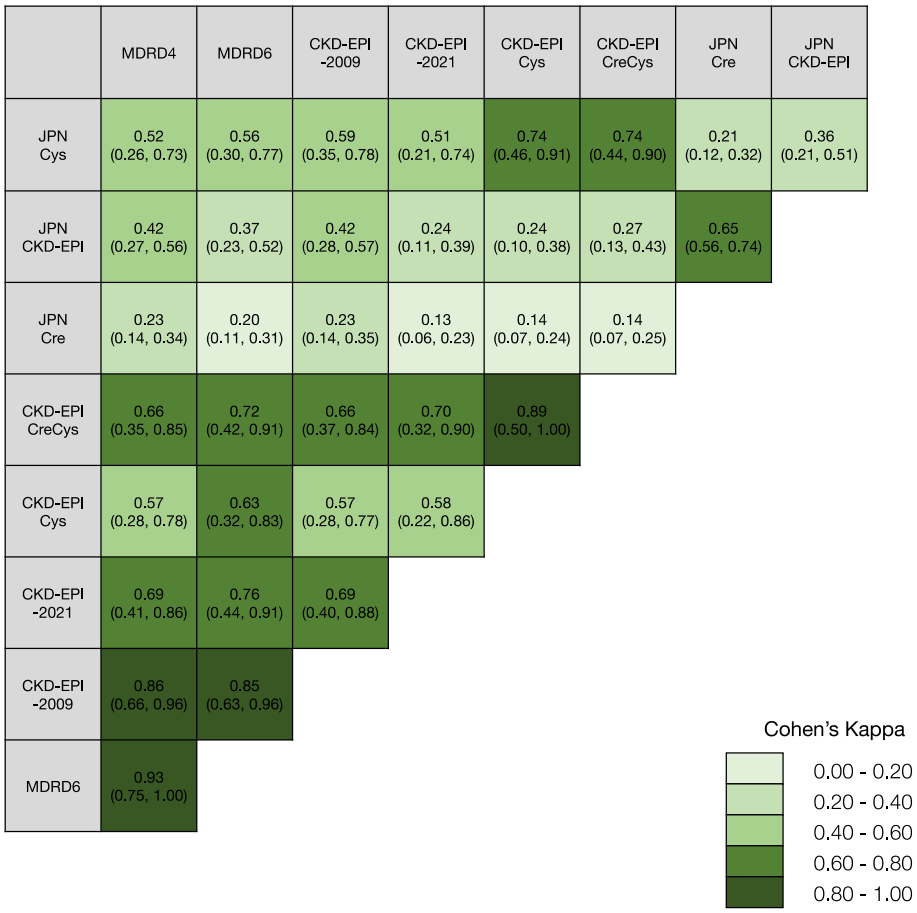

Fig. 3. Agreement of CKD classification between different estimation formulas. The figures in each cell show the unweighted kappa statistics (95% confidence intervals). Greener cells correspond to higher kappa values.

CI: 0.56, 0.74). On the contrary, JPN-Cys had better agreements of CKD classification with other formulas developed in US contexts, although the degree of agreements was poor with JPN-Cre (kappa: 0.21; 95% CI: 0.12, 0.32) and JPN-CKD-EPI (kappa: 0.36; 95% CI: 0.21, 0.51). Supplementary Fig. 1 shows contingency tables and weighted kappa statistics for four GFR categories derived from three different formulas (JPN-Cre, JPN-Cys, and CKD-EPI-2021). As similar to CKD classification mentioned above, JPN-Cre had poor agreements with both JPN-Cys (kappa: 0.13; 95% CI: 0.09, 0.17) and CKD-EPI-2021 (kappa: 0.10; 95% CI: 0.06, 0.13). In contrast, a better agreement of eGFR categories between JPN-Cys and CKD-EPI-2021 was observed in this population (kappa: 0.56; 95% CI: 0.48, 0.64).

4. Discussion

In a sample from the Japanese adults without kidney disease, we calculated eGFR using nine different formulas and compared them against $eGFR_{JPN\text{-}Cre}$, the most commonly used formula in Japan. This descriptive study can provide a finding that the Japanese creatinine-based eGFR value was significantly different from those calculated by the other formulas. This study does not aim to compare with measured GFR and find the best eGFR formula among Japanese, but can describe systematic differences between existing formulas.

Previous studies among Japanese patients suggested that eGFR values from creatinine-based formulas developed in US contexts (MDRD4 and CKD-EPI-20009) were higher compared with the Japanese creatinine-based formula (JPN-Cre) [15]. Our study also confirmed those findings and quantifies the difference being between 20 and 30 ml/min/1.73 m^2 with MDRD4 and CKD-EPI-2009 in individuals who are free from kidney disease. Similar differences are also observed with the novel CKD-EPI formula without the race coefficient, with an average difference of about 23 ml/min/1.73 m^2. Most importantly, the Bland-Altman plots between $eGFR_{JPN\text{-}Cre}$ and eGFR derived from three CKD-EPI formulas (CKD-EPI-2009, CKD-EPI-2021, and CKD-EPI-CreCys) showed a V-shaped curve. This is the worst situation, as it would not only alter any comparison in terms of average distribution and CKD prevalence, but also studies assessing determinants of eGFR levels (e.g., epidemiological association studies, and genome-wide association studies, etc.) may arrive at different conclusions. Additionally, the gaps between $eGFR_{JPN\text{-}Cre}$ and MDRD formulas ($eGFR_{MDRD4}$ and $eGFR_{MDRD6}$) widen monotonically with an increase of eGFR. This systematically increasing difference highlights the cautions when applying the CKD-EPI and MDRD formulas to general Japanese adults.

Integrating the results of the additional analyses shown in Supplementary Fig. 2, we also found 1) the $eGFR_{JPN\text{-}Cre}$ levels were lower than the US creatinine-based formula, whereas we found consistency between the American and Japanese formulas for the cystatin-based formula, and 2) there was a large discrepancy between cystatin and creatinine-based eGFR levels in the Japanese formulas. Unfortunately, although we cannot conclude which formula is the best in this sample due to the lack of measured GFR, we should also consider the possibility that the Japanese creatinine-based formula risks underestimating eGFR in a non-clinical sample. Given that previous clinical studies observed acceptable concordance of measured GFR with eGFR from JPN-Cre and JPN-Cys [15,16], fundamental kidney function for study samples can be attributable to this discrepancy (mean serum creatinine levels: 0.74 mg/dl [this population] vs 1.75 mg/dl [patients in the past studies]). Another possible reason for this discrepancy between JPN-Cre and JPN-

Cys may rely on an individual's physical condition. The difference between $eGFR_{JPN\text{-}Cre}$ and $eGFR_{JPN\text{-}Cys}$ was larger among those who are at higher levels of eGFR, young, and without clinical conditions such as diabetes and hypertension. Therefore, younger people with higher muscle mass had the potential to increase creatinine excretion and then underestimate the eGFR levels by the creatinine-based formula [24]. As for the overestimation by JPN-Cys, it is known that serum levels of cystatin C were higher after drug administration of cyclosporine [25] or with hypothyroidism [26]. Finally, it should be noted that there is an interesting argument about the errors in eGFR values [27,28]. These papers suggested that eGFR values often differ 20–30 ml/min/1.73 m^2 compared with measured GFR. Although we do not have actual measured GFR values to confirm this error, it is possible that the difference of 20–30 ml/min/1.73 m^2 difference might be within this range of error. They also pointed out that these discrepancies between eGFR formulas are resulted in biomarkers (serum creatinine and cystatin C) rather than mathematical problem in eGFR formulas.

There are several limitations to be mentioned. First, we could not determine which formula is the best for eGFR and CKD classification, but this is out of scope in this study. In this study, we tried to summarize how differences have occurred across formulas including a new formula without a race coefficient in a general Japanese population sample. Second, a small sample size has prevented more in-depth analyses involving association with potential determinants of eGFR, stratification, etc. Third, participants in this study were community-dwelling people who were recruited in a local town. The generalizability of the results should be confirmed in other Japanese general population samples and contexts.

In summary, we described systematic differences of eGFR formulas and derived-CKD classification among Japanese adults without kidney disease. Although this descriptive study cannot identify the best eGFR formula, choice of the estimation formula should be careful in clinical settings and academic research.

Author Contributions

N.H. and K.S. were responsible for the design of this study; H.Y., Y.A., H.I., and K.O. collected blood samples and information of participants at study sites; R.F. analyzed data and wrote the paper; Y.I. and K.S. contributed to the analysis and interpretation of data; C.P., Y.T., R.M., G. B., G.D., and S.H. revised the manuscript; all the authors reviewed and approved the final version of the manuscript.

Statements and Declarations

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Fujita Health University (No.HM 19-061).

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Data Sharing Statement

Data is available on request for reasonable reasons.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2022.10.011.

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