Modification of Diet in Renal Disease (MDRD) Study and CKD Epidemiology Collaboration (CKD-EPI) Equations for Taiwanese Adults

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Abstract

Background: Estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) study or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations may not be accurate for Asians; thus, we developed modified eGFR equations for Taiwanese adults.

Methods: This cross-sectional study compared the Taiwanese eGFR equations, the MDRD study, and the CKD-EPI equations with inulin clearance (Cin). A total of 695 adults including 259 healthy volunteers and 436 CKD patients were recruited. Participants from the Kaohsiung Medical University Hospital were used as the development set (N = 556) to develop the Taiwanese eGFR equations, whereas participants from the National Taiwan University Hospital were used as the validation set (N = 139) for external validation.

Results: The Taiwanese eGFR equations were developed by using the extended Bland-Altman plot in the development set. The Taiwanese MDRD equation was 1.309 xMDRD0.912, Taiwanese CKD-EPI was 1.262 xCKD-EPI0.914 and Taiwanese four-level CKD-EPI was 1.205 xfour-level CKD-EPI0.914. In the validation set, the Taiwanese equations had the lowest bias, the Taiwanese equations and the Japanese CKD-EPI equation had the lowest RMSE, whereas the Taiwanese and the Japanese equations had the best precision and the highest P30 among all equations. However, the Taiwanese MDRD equation had higher concordance correlation than did the Taiwanese CKD-EPI, the Taiwanese four-level CKD-EPI and the Japanese equations. Moreover, only the Taiwanese equations had no proportional bias among all of the equations. Finally, the Taiwanese MDRD equation had the best diagnostic performance in terms of ordinal logistic regression among all of the equations.

Conclusion: The Taiwanese MDRD equation is better than the MDRD, CKD-EPI, Japanese, Asian, Thai, Taiwanese CKD-EPI, and Taiwanese four-level CKD-EPI equations for Taiwanese adults.

Introduction

The abbreviated Modification of Diet in Renal Disease (MDRD) study equation [1] was derived from Caucasians and African Americans with chronic kidney diseases (CKD) [2] and is not accurate for Asians [3–6] or when the estimating equations for glomerular filtration rate (eGFR) are above 60 mL/min/1.73 m² [7]. Thus, some Asian countries have developed their own eGFR equations [5,8–11]. However, many equations were derived solely from CKD patients, thereby having limitations in application to the general population [12,13]. For example, the MDRD equation underestimated the gold standard GFR measured by inulin clearance (Cin) for those with Cin of greater than 60 mL/min/1.73 m² in a recent Japanese study [4].

The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation may be more accurate than the MDRD Study equation, particularly at higher levels of GFR and in populations without CKD [14,15]. Thus, the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines recommend using the CKD-EPI equation in adults unless an alternative equation has been shown to be more accurate in the local population [16]. Additionally, the four-level CKD-EPI equation (Black, Asian, Native American and Hispanic, White and other) may improve accuracy for Asians [17].
Taiwan has a high prevalence (11.93%) and a low awareness (3.54%) of CKD [10]. In order to diagnose CKD by an eGFR equation with better accuracy based on the native data, we used C\textsubscript{\text{cr}} as the gold standard to develop modified Taiwanese eGFR equations from a cohort of CKD and healthy people and compared the performance between the original and the modified MDRD Study and the CKD-EPI equations.

**Materials and Methods**

We recruited adults aged over 18 years to sign informed consents from the Kaohsiung Medical University Hospital and the National Taiwan University Hospital. Subjects with acute renal failure, allergy to inulin, pregnancy, problems in voiding, amputation, congestive heart failure, cirrhosis with ascites, use of cimetidine or trimethoprim, oliguria, and those who had ever received any renal replacement therapy were excluded. Healthy volunteers were enrolled according to the percentage of age distribution in Taiwanese reported by the Ministry of the Interior of Taiwan. CKD was diagnosed and classified according to the K/DOQI clinical guidelines [1]. The ratio of the number of the CKD patients to healthy volunteers was approximately 2:1 in this study.

**Ethics Statement**

The study protocol was approved by the Institutional Review Board of the Kaohsiung Medical University Hospital (KMUH-IRB-960304) and National Taiwan University Hospital (NTUH-IRB-201002051M). Informed consents were obtained in written form from patients and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The patients gave consent for the publication of the clinical details.

**Inulin clearance**

All subjects underwent procedures to measure C\textsubscript{\text{cr}} at the Kaohsiung Medical University Hospital or the National Taiwan University Hospital with the same protocol after the approval by the Ethics Committee in each respective hospital. C\textsubscript{\text{cr}} was calculated from serum inulin, urine inulin concentration, and urine volume collected in each time period. The protocol has been described before [9,19]. Briefly, after overnight fasting, the subject drank 500 mL of water 30 minutes before intravenous injection of inulin (40 mL 10% inulin in 360 mL 0.54% NaCl with a final concentration of 1%, Fuji Yakuhin Co. Ltd., Saitama, Japan). Just before the infusion, complete urine collection and blood sampling were performed in an ordinary way. To maintain hydration, 60 mL of water was drunk at 30 and 60 minutes after the start of inulin infusion. The rate of inulin infusion was 300 mL/hour for the first 30 min and 100 mL/hour for the following 60 min.

Blood samples for serum inulin concentration were collected at 45 min and 75 min after the start of inulin infusion. Urine samples for urinary inulin concentration were collected between 30 and 60 min and between 60 and 90 min after the patient completely voided the bladder at 30 min. The first and second urinary excretions of inulin were added, assuming the total amount as a voided the bladder at 30 min. The first and second urinary inulin concentrations were collected between 30 and 60 min, and between 60 and 90 min after the patient completely voided the bladder at 30 min. The first and second urinary excretions of inulin were added, assuming the total amount as a voided the bladder at 30 min. The first and second urinary inulin concentrations were collected between 30 and 60 min, and between 60 and 90 min after the patient completely voided the bladder at 30 min.

The steadystate of serum inulin concentrations was reached at 45 min [22.2 [21.5, 22.9] mg/dL] and 75 min [21.6 [21.1, 22.1] mg/dL] because the coefficient of variation was only 2.9%. This result was similar to a previous study [9].

**Measurement of creatinine and estimated GFR**

Serum creatinine (SCr) was measured by the IDMS-traceable enzymatic method in a Roche Cobas Integra 400 at the Kaohsiung Medical University Hospital. The eGFR values were calculated by the IDMS-traceable MDRD equation: 175 × SCr\textsuperscript{-1.154} × Age\textsuperscript{-0.203} × 0.742 (if female), the CKD-EPI equation: 141 × min(SCr/\kappa, 1)\textsuperscript{0.996} × max(SCr/\kappa, 1)\textsuperscript{0.993} × 0.993\textsubscript{\text{ser}} × 1.018 (if female) where \kappa is 0.7 for females and 0.9 for males, \tau is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/\kappa or 1, and max indicates the maximum of SCr/\kappa or 1, and the four-level CKD-EPI equation [17]: 141 × min(SCr/\kappa, 1)\textsuperscript{0.9} × max(SCr/\kappa, 1)\textsuperscript{−0.210} × 0.993\textsubscript{\text{ser}} × 0.993 [if female] × 1.05 [if Asian] where \kappa is 0.7 for females and 0.9 for males, \tau is −0.328 for females and −0.412 for males, min indicates the minimum of SCr/\kappa or 1, and max indicates the maximum of SCr/\kappa or 1.

Additionally, the Japanese modifications of MDRD (= 0.908 × MDRD) and CKD-EPI (= 0.813 × CKD-EPI) [10], Asian (Chinese, Malays and Indians in Singapore) modifications of MDRD (= 1.086 × MDRD) and CKD-EPI (= 1.049 × CKD-EPI) [11] and Thai modification of MDRD (= 1.129 × MDRD) [20] were calculated.

**Statistical analysis**

Continuous data were expressed as the mean ± standard error of the mean or mean (95% confidence interval) unless stated otherwise. Linear regression was expressed as the prediction equation ± standard deviation of prediction. The 95% prediction interval was calculated as the estimate ± 2 standard deviations of prediction. Note that the 95% prediction interval is always wider than the 95% confidence interval because the former estimates the scatter of the data whereas the latter estimates only the mean [21]. Continuous variables were compared by unpaired t-tests whereas categorical variables were compared by $\chi^2$ tests unless stated otherwise. All eGFR equations were compared to the Taiwanese MDRD equation.

The Taiwanese equations were generated from the whole development set by using linear regression of the difference on the average (i.e. the extended Bland-Altman plot in the MethComp package in R, which was designed specifically for method comparison studies) [22] of the log-transformed C\textsubscript{\text{cr}} and the MDRD, CKD-EPI and four-level CKD-EPI equations.

Internal validation of the Taiwanese equations was performed by 2,000 bootstraps in which the subjects were drawn at random with replacement [23]. Hence, subjects may be represented zero or many times in a bootstrap sample. The Taiwanese equations were trained in the sampled subjects and tested in the original development set in each bootstrap step. Afterwards, the difference of RMSE between the bootstrap and the test samples was subtracted from the RMSE of the original development set [23].

For the validation set, eGFR equations were assessed for accuracy and agreement. Accuracy was measured as the percentage within 30% of C\textsubscript{\text{cr}} (P30), bias, precision, and the root mean squared error (RMSE) [24]. The bias was defined as the median difference between C\textsubscript{\text{cr}} and eGFR (C\textsubscript{\text{cr}} - eGFR) with negative values indicating overestimation of C\textsubscript{\text{cr}}. Precision was expressed as the interquartile range of the bias. RMSE was defined as the square root of the average squared difference of C\textsubscript{\text{cr}} and eGFR. RMSE was compared by using 2,000 bootstrap samples to derive the standard errors of the differences of RMSE [11].
Because $P_{50}$ and bias were compared between the paired data, $P_{50}$ was compared by the exact McNemar test, whereas bias was compared by the Wilcoxon signed rank test.

Agreement between two continuous variables ($C_m$ and eGFR) was measured by the concordance correlation coefficient ($r$) [25] and the Bland-Altman plot [22,26]. Concordance correlation was compared by Zou’s method [27]. Note that the comparison of two $r$’s ($r$ of $C_m$ and eGFR1 and $r$ of $C_m$ and eGFR2) requires a third $r$ ($r$ of eGFR1 and eGFR2). Diagnostic performance of the eGFR equations for the classification of CKD stages (according to $C_m$, or eGFR alone, disregarding proteinuria) was assessed by ordinal logistic (generalized ordered logit) regression and chance-corrected agreement (kappa coefficient, a measure of the agreement between two categorical variables) [28]. Ordinal logistic regressions (Cin or eGFR alone, disregarding proteinuria) was assessed by ordinal logistic (generalized ordered logit) regression and chance-corrected agreement (kappa coefficient, a measure of the agreement between two categorical variables) [28]. Ordinal logistic regressions ($C_m$-defined CKD category and eGFR was the dependent and independent variable, respectively) (Methods S1) were compared by the Akaike information criterion (AIC) where a model with the lowest AIC is the best model [29]. Note that the AIC is an information-theoretic approach in which there are no null hypothesis significance tests to choose the lowest AIC [29]. Instead, the Akaike weight ($w_i$) is used to weigh the evidence of each model [29,30].

$$w_i = \frac{\exp\left(-\frac{AIC_i - \min(AIC)}{2}\right)}{\sum_{k=1}^{K} \exp\left(-\frac{AIC_k - \min(AIC)}{2}\right)}$$

Here, $\exp$ denotes the exponential, $AIC_i$ denotes the AIC for the $i$th model whereas $\min(AIC)$ denotes the minimal AIC for the $K$ models.

Analyses were computed by using the R (version 3.0.0; Free Software Foundation, Boston, MA) and the Stata software (version 13.0, StataCorp LP, College Station, TX).

**Results**

**Characteristics of the Participants in the Development and Validation Sets**

From April, 2008 to October, 2009, a total of 300 persons were recruited from the Kaohsiung Medical University Hospital where 11 subjects were excluded due to incomplete data. From Oct. 2009 to June 2011, a total of 406 persons were recruited from either the Kaohsiung Medical University Hospital or the National Taiwan University Hospital. Thus, a total of 695 participants which included 259 healthy volunteers and 436 CKD patients were recruited.

Participants from the Kaohsiung Medical University Hospital (located in the southern Taiwan) were used as the development set ($N = 556$) to develop the Taiwanese eGFR equations whereas participants from the National Taiwan University Hospital were used as the validation set ($N = 139$) for the external validation of the Taiwanese eGFR equations. Note that this was a geographical external validation set [31], in that the National Taiwan University Hospital is a different hospital located in Northern Taiwan. As shown in Table 1, there were no healthy volunteers, and the participants were older in the validation set.

**Determination and bootstrap cross-validation of the Taiwanese eGFR equations in the development set**

Taiwanese eGFR equations were determined by using linear regression of the difference on the average (i.e. the extended Bland-Altman plot) in the development set [22]. Taiwanese eGFR equations were $1.309 \times \text{MDRD}^{0.912}$ for the Taiwanese MDRD (Fig. 1A), $1.262 \times \text{CKD-EPI}^{0.914}$ for the Taiwanese CKD-EPI (Fig. 1B) and $1.205 \times \text{four-level CKD-EPI}^{0.913}$ for the Taiwanese four-level CKD-EPI (Fig. 1C) in the [anti-logged] original units, respectively. In 2,000 bootstraps of the development set, RMSE of the Taiwanese MDRD (11.7) was lower than that of the Taiwanese CKD-EPI (13.7) and Taiwanese four-level CKD-EPI (18.3). Note that RMSE of internal validation was lower than that of the external validation. However, the results of internal validation are usually too optimistic and external validation is necessary for the generalizability of prediction rules [32].

**Accuracy of eGFR for the validation set**

Accuracy was assessed by $P_{50}$, bias, precision and the RMSE. We found $P_{50}$ for all of the equations except that of the Japanese equations. Taiwanese CKD-EPI or Taiwanese four-level CKD-EPI equations was lower than that of the Taiwanese MDRD equation for the whole set (Table 2) and those with $C_{m} \geq 60$ mL/min/1.73 m$^2$ (Table 3). In contrast, only $P_{50}$ of the four-level CKD-EPI, Asian CKD-EPI and Thai MDRD equations were lower than that of the Taiwanese MDRD equation for those with $C_{m} < 60$ mL/min/1.73 m$^2$ (Table 4).

The Taiwanese equations had the lowest bias among all of the equations for the whole set (Table 2), those with $C_{m} \geq 60$ mL/min/1.73 m$^2$ (Table 3) and those with $C_{m} < 60$ mL/min/1.73 m$^2$ (Table 4). The Taiwanese and the Japanese equations had the best precision (19–20 mL/min/1.73 m$^2$) among all of the equations for the whole set (Table 2). The Taiwanese equations, the Japanese CKD-EPI equation, and the MDRD equation had the lowest RMSE among all equations for the whole set (Table 2). In contrast, the Taiwanese MDRD equation and the Japanese equations had the lowest RMSE for those with $C_{m} < 60$ mL/min/1.73 m$^2$ (Table 4). However, the Taiwan MDRD equation had lower RMSE than did all equations except the Taiwanese CKD-EPI, Taiwanese four-level CKD-EPI, MDRD and CKD-EPI equations for those with $C_{m} \geq 60$ mL/min/1.73 m$^2$ (Table 3).

**Agreement between $C_m$ and eGFR for the validation set**

The agreement between $C_m$ and the eGFR equations was assessed by concordance correlation and the Bland-Altman plot for the validation set. We found that concordance correlation of the Taiwanese MDRD equation (0.823) was higher ($P < 0.05$) than those of the Japanese MDRD (0.803), Taiwanese CKD-EPI (0.78), Taiwanese four-level CKD-EPI (0.78), Thai MDRD (0.772) and Japanese CKD-EPI (0.771) equations, but was not different from that of the MDRD (0.826), CKD-EPI (0.798), Asian MDRD (0.794), Asian CKD-EPI (0.782), or four-level CKD-EPI (0.781), for the whole set.

The concordance correlation of the Taiwanese MDRD equation (0.757) was higher ($P < 0.05$) than those of the Taiwanese CKD-EPI (0.729), Taiwanese four-level CKD-EPI (0.728), MDRD (0.685), CKD-EPI (0.628), Asian MDRD (0.627), Asian CKD-EPI (0.593), four-level CKD-EPI (0.59) and Thai MDRD (0.598) equations, but was not different from that of the Japanese MDRD (0.771) or Japanese CKD-EPI (0.746) equation, for those with $C_{m} < 60$ mL/min/1.73 m$^2$.

The concordance correlation of the Taiwanese MDRD (0.537) was higher ($P < 0.05$) than those of the Taiwanese four-level CKD-EPI (0.39) and Taiwanese CKD-EPI (0.388) and Japanese CKD-EPI (0.378) equations, but was not different from that of the MDRD (0.571), Asian MDRD (0.522), Japanese MDRD (0.502), Thai MDRD (0.489), CKD-EPI (0.464), four-level CKD-EPI (0.447) or Asian CKD-EPI (0.446), for those with $C_{m} \geq 60$ mL/min/1.73 m$^2$. 

Taiwanese eGFR Equations
In the Bland-Altman plot of the original data (data not shown), there were increasing scatters of differences with increasing eGFR (i.e., V-shaped limits of agreement) for all of the equations. Moreover, there were negative correlations between the difference and the mean for the MDRD, CKD-EPI and four-level CKD-EPI equations respectively. These findings violated the assumptions of the homogeneity of the scatter of differences and a constant bias for the Bland-Altman plot [22,26,33]. Thus, the Bland-Altman plot of the difference of the log-transformed data on the ordinate [33] was shown in Fig. 2. Note that the anti-log of the difference between two log-transformed data is the ratio of the two data in the original units. The geometric mean ratio (95% limits of agreement) in the original units of the Taiwanese MDRD (A), Taiwanese CKD-EPI (B), Taiwanese four-level CKD-EPI (C), MDRD (D), CKD-EPI (E) and four-level CKD-EPI (F) equations was 1.023 (0.58, 1.79), 1.025 (0.57, 1.8), 1.025 (0.57, 1.8), 0.93 (0.5, 1.7), 0.91 (0.49, 1.7), 0.86 (0.46, 1.6), respectively.

Regression lines and the 95% prediction intervals of the Taiwanese and Japanese equations are shown in Figs. 3A to 3F. The Taiwanese and the Japanese equations had very low bias in that the Taiwanese equations had lower biases than those of the Japanese equations for those with Cin 60 mL/min/1.73 m². Note that P30 is an arbitrary measure of accuracy whereas dichotomization (i.e., P 30) of continuous variables introduces biases [34]. In contrast, bias and RMSE are standard in ordinal logistic regression, the Taiwanese MDRD equation had the lowest AIC (230.7) compared to those of the MDRD (231.4), CKD-EPI (232), four-level CKD-EPI (232.2), Taiwanese CKD-EPI (231.4), Japanese CKD-EPI (231.5), Japanese MDRD (231.4), Japanese CKD-EPI (232), Asian MDRD (231.4), Asian CKD-EPI (232) and Thai MDRD (231.4) equations. Moreover, the Taiwanese MDRD equation had the highest Akaike weight (0.14) compared to those of the MDRD (0.097), CKD-EPI (0.07), four-level CKD-EPI (0.07), Taiwanese CKD-EPI (0.098), Taiwanese four-level CKD-EPI (0.09), Japanese MDRD (0.097), Japanese CKD-EPI (0.07), Asian MDRD (0.097), Asian CKD-EPI (0.07) and Thai MDRD (0.097) equations. Thus, the Taiwanese MDRD equation had the best diagnostic performance.

Discussion

In this study, the Taiwanese equations had the lowest bias, the Taiwanese equations and the Japanese CKD-EPI equation had the lowest RMSE, the Taiwanese and the Japanese equations had the best precision and the highest P30. The Taiwanese MDRD equation had higher concordance correlation than the Taiwanese CKD-EPI, Taiwanese four-level CKD-EPI and the Japanese equations. Moreover, only the Taiwanese equations had no proportional bias among all of the equations. Finally, the Taiwanese MDRD equation had the best diagnostic performance in terms of ordinal logistic regression among all of the equations.

We found that the MDRD, CKD-EPI, four-level CKD-EPI, Asian equations, and Thai MDRD equations overestimated GFR, whereas the Japanese equations underestimated GFR. In contrast, the Taiwanese equations had very low bias in that the Taiwanese equations had the lowest bias among all equations.

The Taiwanese and the Japanese equations had similar performances in terms of P30 and precision in that they had the highest P30 and the best precision among all equations. Moreover, the Taiwanese equations and the Japanese CKD-EPI equation had the lowest RMSE among all equations. However, the Taiwanese equations had lower biases than those of the Japanese equations and the Taiwanese MDRD equation had lower RMSE than those of the Japanese equations for those with C\textsubscript{in} >60 mL/min/1.73 m². Note that P30 is an arbitrary measure of accuracy whereas dichotomization (i.e., P 30) of continuous variables introduces biases [34]. In contrast, bias and RMSE are standard.

### Table 1. Clinical characteristics of the participants.

| Clinical characteristics | Development set (n = 556) | Validation set (n = 139) | P |
|--------------------------|---------------------------|--------------------------|---|
| Age (years)              | 47 ± 0.7                  | 51 ± 1                   | 0.006 |
| Men (%)                  | 47.1                      | 51                       | 0.40 |
| Height (cm)              | 163 ± 0.4                 | 163 ± 0.8                | 0.96 |
| Weight (kg)              | 64 ± 0.5                  | 62 ± 1                   | 0.14 |
| Body surface area (m²)   | 1.69 ± 0.01               | 1.67 ± 0.01              | 0.28 |
| CKD clinic patient (%)   | 53.4                      | 100.0                    | <0.001 |
| Diabetes mellitus (%)    | 12.0                      | 12.2                     | 0.95 |
| Serum creatinine (mg/dL) | 1.52 ± 0.05               | 1.43 ± 0.1               | 0.68 |
| C\textsubscript{in} (mL/min/1.73 m²) | 67 ± 1.6                 | 68.8 ± 3.0               | 0.56 |
| C\textsubscript{in}<60 mL/min/1.73 m² (%) | 43.5                     | 42.5                     | 0.82 |

Abbreviations: CKD, chronic kidney disease; C\textsubscript{in}, inulin clearance.

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measures of model accuracy [35]. Moreover, the Taiwanese MDRD equation had higher concordance correlation than the Japanese equations. Finally, the Japanese, but not the Taiwanese equations, had proportional bias. Thus, the Taiwanese MDRD equation is better than the Japanese equations.

In the Bland-Altman plot, the 95% limits of agreement were too wide to draw conclusions. Nonetheless, only the Taiwanese equations had no proportional bias among all equations in the extended Bland-Altman plot [22].

Surprisingly, the Taiwanese MDRD equation had similar kappa value with the other equations. This finding can be explained by the fact that eGFR is a continuous variable and that the eGFR-defined CKD stage is an arbitrary categorical variable whereas dichotomization of continuous predictor variables introduces biases [34]. In contrast, the Taiwanese MDRD equation-derived eGFR (a continuous variable) had the best diagnostic performance in terms of the lowest AIC and the highest Akaike weight in the ordinal logistic regression.

Many (but not all) studies found that the CKD-EPI equation was more accurate than the MDRD equation [6,24,36-38]. For example, the Japanese CKD-EPI equation was better than the Japanese MDRD equation [10]. The CKD-EPI equation was also better than the MDRD and four-level CKD-EPI equations in a Chinese study [39]. However, the CKD-EPI equation was not

Figure 1. Determination of the Taiwanese eGFR equations in the development set. Taiwanese eGFR equations were derived by using linear regression of the differences on the average (i.e. the extended Bland-Altman plot). Cᵢ and the eGFR equations were log-transformed and plotted on the log-scale. The regression line (thin solid line) and its 95% prediction interval (dotted lines) were plotted along with the identity (thick solid diagonal) line. (A) The regression equation of the Taiwanese MDRD equation was 1.309×MDRD⁰.⁹¹² in the (anti-logged) original unit. (B) The regression equation of the Taiwanese CKD-EPI equation was 1.262×CKD-EPI⁰.⁹¹⁴ in the original unit. (C) The regression equation of the Taiwanese four-level CKD-EPI equation was 1.205×four-level CKD-EPI⁰.⁹¹⁴ in the original unit.
The Taiwanese CKD-EPI and Taiwanese four-level CKD-EPI equations were worse than the Taiwanese MDRD equation especially for those with Cin < 60 mL/min/1.73 m². The differences in ethnicity, study population and the use of different reference GFR methods may account for this discrepancy. For example, our study and the Japanese study [10] used the gold standard Cin as the reference GFR, whereas the MDRD and CKD-EPI equation used urinary clearance of iothalamate, which overestimates Cin [40-42]. In contrast, the Singapore and the Thai studies [11,20] used plasma technetium-99m-labeled diethylene-triamine penta-acetate (99mTc-DTPA) clearance, which also overestimates Cin [43,44].

The strengths of this study were the use of the gold standard (Cin) as the reference GFR, the inclusion of healthy volunteers, and the validation of the Taiwanese eGFR equations using an external validation set. One of the limitations of this study was that there were no healthy volunteers in the validation set. However, the mean Cin was similar and the proportion of subjects with Cin < 60 mL/min/1.73 m² was also similar between the development and the validation set. The other limitation was that the participants were older in the external validation set. However, differences in case mix is not a great concern for external

### Table 2. Performance of the eGFR equations for the validation set.

| Equation          | P₃₀ (%) | Bias (mL/min/1.73 m²) | Precision (mL/min/1.73 m²) | RMSE (mL/min/1.73 m²) | Kappa |
|-------------------|---------|-----------------------|----------------------------|-----------------------|-------|
| MDRD              | 63.3    | −5.4**                | 23                         | 23.3                  | 0.437 |
| CKD-EPI           | 60.4**  | −8.0**                | 25                         | 24.2**                | 0.38  |
| Four-level CKD-EPI| 52.5**  | −12.0**               | 29                         | 26.1**                | 0.38  |
| Japanese MDRD     | 71.2    | 5.8**                 | 19                         | 23.7**                | 0.48  |
| Japanese CKD-EPI  | 70.5    | 4.0**                 | 20                         | 23.4                  | 0.494 |
| Asian MDRD        | 56.8**  | −11.0**               | 28                         | 27.0**                | 0.435 |
| Asian CKD-EPI     | 54.0**  | −11.0**               | 28                         | 26.0**                | 0.38  |
| Thai MDRD         | 52.5**  | −14.0**               | 32                         | 29.0**                | 0.435 |
| Taiwanese MDRD    | 73.4    | 0.17                  | 19                         | 21.4                  | 0.495 |
| Taiwanese CKD-EPI | 73.4    | 0.42                  | 20                         | 23.0                  | 0.549 |
| Taiwanese four-level CKD-EPI | 74.1 | 0.24 | 20 | 23.0 | 0.549 |

Abbreviations and definitions: MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; P₃₀, the percentage within 30% of inulin clearance; bias, median difference of inulin clearance and estimated GFR (Cin – eGFR); precision, interquartile range of the bias; RMSE, root mean square error; Kappa, kappa coefficients of the eGFR equations for the classification of CKD stages.

### Table 3. Performance of the eGFR equations for the participants with Cin ≥ 60 mL/min/1.73 m² in the validation set.

| Equation          | P₃₀ (%) | Bias (mL/min/1.73 m²) | Precision (mL/min/1.73 m²) | RMSE (mL/min/1.73 m²) | Kappa |
|-------------------|---------|-----------------------|----------------------------|-----------------------|-------|
| MDRD              | 65.0**  | −9.2**                | 30                         | 27.0                  | 0.257 |
| CKD-EPI           | 65.0**  | −12.0**               | 26                         | 26.7                  | 0.205 |
| Four-level CKD-EPI| 57.5**  | −16.6**               | 26                         | 28.4**                | 0.205 |
| Japanese MDRD     | 78.8    | 8.6**                 | 26                         | 27.9**                | 0.28  |
| Japanese CKD-EPI  | 81.3    | 5.2**                 | 26                         | 28.7**                | 0.29  |
| Asian MDRD        | 60.0**  | −17.0**               | 30                         | 31.1**                | 0.26  |
| Asian CKD-EPI     | 57.5**  | −16.0**               | 26                         | 28.3**                | 0.26  |
| Thai MDRD         | 55.0**  | −22.0**               | 31                         | 33.9**                | 0.26  |
| Taiwanese MDRD    | 81.3    | 2.1                   | 28                         | 25.8                  | 0.271 |
| Taiwanese CKD-EPI | 81.3    | 1.2                   | 26                         | 27.5                  | 0.33  |
| Taiwanese four-level CKD-EPI | 81.3 | 1.4 | 26 | 27.5 | 0.33 |

Abbreviations and definitions: MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; P₃₀, the percentage within 30% of inulin clearance; bias, median difference of inulin clearance and estimated GFR (Cin – eGFR); precision, interquartile range of the bias; RMSE, root mean square error; Kappa, kappa coefficients of the eGFR equations for the classification of CKD stages.

*P<0.05 versus Taiwanese MDRD; **P<0.01 versus Taiwanese MDRD; ***P<0.001 versus Taiwanese MDRD.

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| Equation          | P30 (%) | Bias (mL/min/1.73 m²) | Precision (mL/min/1.73 m²) | RMSE (mL/min/1.73 m²) | Kappa |
|-------------------|---------|-----------------------|-----------------------------|-----------------------|-------|
| MDRD              | 61.0    | −1.7**                | 17                          | 17.0**                | 0.356 |
| CKD-EPI           | 54.0    | −3.1**                | 21                          | 20.3**                | 0.31  |
| Four-level CKD-EPI | 45.8*  | −5.0**                | 24                          | 22.6**                | 0.31  |
| Japanese MDRD     | 61.0    | 3.9                   | 13                          | 12.3                  | 0.424 |
| Japanese CKD-EPI  | 56.0    | 2.4**                 | 15                          | 13.9                  | 0.407 |
| Asian MDRD        | 52.5    | −4.8**                | 21                          | 20.2**                | 0.365 |
| Asian CKD-EPI     | 49.0*   | −5.1**                | 24                          | 22.4**                | 0.291 |
| Thai MDRD         | 49.0*   | −5.6**                | 23                          | 21.9**                | 0.365 |
| Taiwanese MDRD    | 62.7    | −0.58                 | 15                          | 13.2                  | 0.429 |
| Taiwanese CKD-EPI | 62.7    | −0.61                 | 15                          | 14.7                  | 0.411 |
| Taiwanese four-level CKD-EPI | 64.4 | −0.62 | 15 | 14.8 | 0.411 |

Abbreviations and definitions: MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; P30, the percentage within 30% of inulin clearance; bias, median difference of inulin clearance and estimated GFR (Cin – eGFR); precision, interquartile range of the bias; RMSE, root mean square error; Kappa, kappa coefficients of the eGFR equations for the classification of CKD stages.

*P<0.05 versus Taiwanese MDRD;
**P<0.01 versus Taiwanese MDRD;
***P<0.001 versus Taiwanese MDRD.

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Figure 2. Bland-Altman plot of eGFR equations versus inulin clearance (Cin) for the validation set. The difference of log-transformed Cin and eGFR equation (ordinate) was plotted against the mean of Cin and each respective eGFR equation (abscissa). The mean difference was shown as a dotted horizontal line whereas the 95% limit of agreement was shown as the shaded area. Note that the anti-log of the difference between two log-transformed data is the ratio of the two data in the original units. Bland-Altman plot of (A) The geometric mean ratio (95% limit of agreement) was 1.023 (0.58, 1.79) for the Taiwanese MDRD in the original unit, (B) The geometric mean ratio (95% limit of agreement) was 1.025 (0.57, 1.8) for the Taiwanese CKD-EPI in the original unit, (C) The geometric mean ratio (95% limit of agreement) was 1.025 (0.57, 1.8) for the Taiwanese four-level CKD-EPI, (D) The geometric mean ratio (95% limit of agreement) was 1.025 (0.57, 1.8) for the MDRD in the original unit, (E) The geometric mean ratio (95% limit of agreement) was 0.93 (0.5, 1.7) for the CKD-EPI in the original unit and (F) The geometric mean ratio (95% limit of agreement) was 0.86 (0.46, 1.6) for the four-level CKD-EPI in the original unit.

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Finally, both hospitals used the same study protocol and serum creatinine and inulin were both measured at the Kaohsiung Medical University Hospital. In conclusion, the Taiwanese MDRD equation performs better than the MDRD, CKD-EPI, four-level CKD-EPI, Japanese, Asian, Thai, Taiwanese CKD-EPI, and Taiwanese four-level CKD-EPI equations for Taiwanese adults. Thus, further studies are required to determine its clinical applications (e.g. correlations with complications and prognosis) in Taiwan.

Supporting Information

Figure S1 Logistic regression for $C_{\text{in}}$-defined CKD stage 1 in the validation set. $C_{\text{in}}$ and the eGFR equations were log-transformed and plotted on the log-scale in the regression derived from the extended Bland-Altman plot. The regression line (thin solid line) and its 95% prediction interval (dotted lines) were plotted along with the identity (thick solid diagonal) line. (A) The slope (95% confidence interval) was 0.99 (0.92, 1.06) and the regression equation of the Taiwanese MDRD was $1.06 \times \text{Taiwanese MDRD}^{0.99}$ in the anti-logged (original) unit. (B) The slope was 1.008 (0.93, 1.08) and the regression equation of the Taiwanese CKD-EPI was $0.99 \times \text{Taiwanese CKD-EPI}^{1.01}$ in the original unit. (C) The slope was 1.007 (0.93, 1.08) and the regression equation of the Taiwanese four-level CKD-EPI was $0.99 \times \text{Taiwanese four-level CKD-EPI}^{1.01}$ in the original unit. (D) The slope was 0.9 (0.83, 0.96) and the regression equation of the MDRD equation was $1.41 \times \text{MDRD}^{0.9}$ in the original unit. (E) The slope was 0.92 (0.85, 0.99) and the regression equation of the CKD-EPI equation was $1.28 \times \text{CKD-EPI}^{1.01}$ in the original unit. (F) The slope was 0.92 (0.85, 0.99) and the regression equation of the four-level CKD-EPI was $1.22 \times \text{four-level CKD-EPI}^{1.02}$ in the original unit.

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Figure 3. Regression of the Taiwanese eGFR equations versus inulin clearance ($C_{\text{in}}$) in the validation set. $C_{\text{in}}$ and the eGFR equations were log-transformed and plotted on the log-scale in the regression derived from the extended Bland-Altman plot. The regression line (thin solid line) and its 95% prediction interval (dotted lines) were plotted along with the identity (thick solid diagonal) line. (A) The slope (95% confidence interval) was 0.99 (0.92, 1.06) and the regression equation of the Taiwanese MDRD was $1.06 \times \text{Taiwanese MDRD}^{0.99}$ in the anti-logged (original) unit. (B) The slope was 1.008 (0.93, 1.08) and the regression equation of the Taiwanese CKD-EPI was $0.99 \times \text{Taiwanese CKD-EPI}^{1.01}$ in the original unit. (C) The slope was 1.007 (0.93, 1.08) and the regression equation of the Taiwanese four-level CKD-EPI was $0.99 \times \text{Taiwanese four-level CKD-EPI}^{1.01}$ in the original unit. (D) The slope was 0.9 (0.83, 0.96) and the regression equation of the MDRD equation was $1.41 \times \text{MDRD}^{0.9}$ in the original unit. (E) The slope was 0.92 (0.85, 0.99) and the regression equation of the CKD-EPI equation was $1.28 \times \text{CKD-EPI}^{1.01}$ in the original unit. (F) The slope was 0.92 (0.85, 0.99) and the regression equation of the four-level CKD-EPI was $1.22 \times \text{four-level CKD-EPI}^{1.02}$ in the original unit.

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Figure S2 Ordinal logistic regression of the Taiwanese MDRD equation for the prediction of $C_{\text{in}}$-defined CKD stages in the validation set. Ordinal logistic regression (generalized ordered logit) of the Taiwanese MDRD equation was performed by the cumulative logit model. (A) Cumulative probability of $C_{\text{in}}$-defined CKD stages and the logistic curves. Note that the cumulative probability of CKD stage 1, stage 1–2, stage 1–3 and stage 1–4 increases as eGFR increases. (B) Taiwanese MDRD equation was used to predict the log(odds) (logit) of the probability of CKD stage 1, stage 1–2, stage 1–3 and stage 1–4. Note that the non-linear relationship between cumulative probability and eGFR in (A) had been transformed to be a linear ($\pi+\beta x$) relationship. The odds ratio (95% confidence interval) of one unit increase in x was calculated as $\exp(\beta)$, which...
was 1.09 (1.03, 1.13), 1.11 (1.07, 1.15), 1.14 (1.08, 1.21) and 2.01 (1.06, 3.82) for stage 1, stage 1–2, stage 1–3 and stage 1–4, respectively.

**Methods S1 Supplemental methods-ordinal logistic regression.**

(DOC)

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**Author Contributions**

Conceived and designed the experiments: L-IC, J-YG-HCC. Performed the experiments: L-IC, J-YG-HCC T-HC Y-MC K-DW. Analyzed the data: J-YG. Contributed reagents/materials/analysis tools: M-CK S-JH T-HC Y-MC K-DW. Wrote the paper: L-IC, J-YG.