

# Influence of Weight-Age Normalization on Glomerular Filtration Rate Values of Renal Patients

## A STROBE-Compliant Article

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**Abstract:** To explore whether weight-age (W-A) could be applied in clinical practice, this study was designed to verify the normalization ability of W-A by the data from another medical center, and to assess the influence of the normalization on glomerular filtration rate (GFR) values in renal patients.

Both plasma clearance (pGFR) and camera-based (gGFR), which were separately scaled to W-A and body surface area (BSA), were measured for patients with diffuse renal diseases. The patients ( $n = 298$ ) were stratified according to the Chinese body mass index (BMI) criteria and were staged according to the Kidney Disease Outcome Quality Initiatives guideline based on gGFR and pGFR separately.

The indices of intraclass correlation coefficient (ICC), concordance correlation coefficient (CCC), and ratio of residual standard deviation to pooled standard deviation (RSD/PSD) suggested that, for all patients and each BMI stratum, W-A was obviously better than BSA in scaling GFR. Both under pGFR or gGFR renal stages, only small amount of the patients encountered stage migrations from BSA to W-A scaled stages. The differences between any 2 of the unscaled, BSA scaled, and W-A scaled gGFR (or pGFR) were not obviously changed. Additionally, in some strata, W-A normalization is better than BSA normalization in decreasing the median bias between pGFR and gGFR.

W-A is better than BSA in scaling GFR without obvious modifying GFR values and can be applied in routine clinical practice.

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**Abbreviations:** BMI = body mass index, BSA = body surface area, CCC = concordance correlation coefficient, GFR = glomerular filtration rate, gGFR = camera-based glomerular filtration rate, ICC = intraclass correlation coefficient, pGFR = plasma clearance glomerular filtration rate, W-A = Weight-Age.

## INTRODUCTION

Normalization is intended to facilitate the comparison of glomerular filtration rate (GFR) among individuals with different body sizes. Especially, comparing an individual's GFR to the normal reference range of general population can be conceived as assessing the extent of renal damage.<sup>1</sup> Therefore, scaling GFR to a less powerful variable may result in wrong critical values, and mislead the clinical evaluation.<sup>2</sup>

Since McIntosh et al<sup>3</sup> proposed that an individual's body surface area (BSA) linearly correlated with GFR, the BSA normalization (ratio method) has been gradually applied worldwide in scaling GFR.<sup>3,4</sup> In recent years, the linear correlation between BSA and GFR was debated, and subsequent studies proposed other variables to scale GFR, for example, total body water and metabolic rate.<sup>4,5</sup> However, all these variables do not linearly correlate well to plasma clearance in healthy population.<sup>6</sup>

Based on the linear correlation between index variable and GFR, a previous study regressed an index variable of weight-age (W-A), which performed better than BSA in scaling GFR of healthy individuals.<sup>7</sup> Although W-A is a potential substitute for BSA in scaling GFR, the variable should be validated before applying in clinical practice for the following reasons. First, current renal staging criteria grouped patients with GFR value indexed to BSA and was widely used in clinical studies. Therefore, W-A normalization should not obviously change the stage criteria, which directly related to our clinical observation on renal diseases.<sup>7</sup> Second, because of the possibility of water-sodium retention in renal patients, it is not sure whether the new variable could be used in these patients.<sup>5</sup>

Typically, in quantifying GFR, systematic bias, random variation, and possible renal damage are the influence factors.<sup>5</sup> The goal of normalization is to mainly reduce the between-subject variability, which is included in random variation, such that the normalized GFR is more easily compared. Therefore, to take into account the 3 factors simultaneously, the repeated measures analyses are more appropriate. In other words, analysis between repeatedly measured GFRs can differentiate systematic bias and random variation, and can parallel measure the damaged GFRs.<sup>5,8</sup>

Above all, using data from another independent medical center, this study was designed to verify the normalization ability of W-A in renal patients and to assess the influence of the normalization on GFR values.

TABLE 1. Patient Information

	All Patients	Strata A (n = 161)	Strata B(n = 90)	Strata C (n = 47)
Age, year	51.5 ± 16.6	49.7 ± 17.4	52.6 ± 16.3	55.5 ± 13.4
Weight, kg	65.6 ± 11.7**	59.1 ± 7.9	69.0 ± 7.8	81.4 ± 11.0
Height, cm	165.2 ± 8.4	165.4 ± 7.9	164.5 ± 8.7	166.0 ± 9.7
BSA, m <sup>2</sup>	1.72 ± 0.18**	1.65 ± 0.14	1.75 ± 0.15	1.89 ± 0.18
W-A	3.42 ± 0.58**	3.29 ± 0.56	3.50 ± 0.57	3.74 ± 0.52
BMI, kg/m <sup>2</sup>	23.9 ± 3.3**	21.5 ± 1.8	25.4 ± 0.9	29.4 ± 2.0
gGFR, mL/min	45.6 ± 25.3	44.1 ± 26.3	48.3 ± 23.5	45.8 ± 25.3
pGFR, mL/min	47.4 ± 30.1	47.0 ± 31.1	46.8 ± 28.6	49.7 ± 29.9

Patients are grouped into strata A (BMI < 23.9 kg/m<sup>2</sup>), strata B (24.0 < BMI < 26.9 kg/m<sup>2</sup>), and strata C (BMI ≥ 27.0 kg/m<sup>2</sup>). Significant difference between BMI strata. \**P* < 0.05, \*\**P* < 0.01. BMI = body mass index, BSA = body surface area, gGFR = camera-based glomerular filtration rate, pGFR = plasma clearance glomerular filtration rate, W-A = weight-age.

## METHODS

### Patients

During 2010 to 2014, patients suffering from diffuse renal diseases were enrolled. The inclusion criterion was age older than 18 years, and all individuals had signed informed consent upon the enrollment. Patients with a history of hydronephrosis were excluded in this study. All individuals accepted <sup>99m</sup>Tc-diethylene triamine pentaacetic acid (<sup>99m</sup>Tc-DTPA) renography (Gates method, gGFR) and plasma clearance (pGFR) examinations, and body weight and height were measured before the examinations on a calibrated scale. According to the Kidney Disease Outcome Quality Initiatives guideline, the patients were separately staged based on BSA (or W-A) scaled pGFR and gGFR.<sup>9</sup> Additionally, considering the influence of body mass index (BMI) on GFR normalization, the recruited patients were stratified according to the Chinese BMI criteria:<sup>10</sup> stratum A (BMI < 23.9 kg/m<sup>2</sup>), stratum B (24.0 < BMI < 26.9 kg/m<sup>2</sup>), and stratum C (BMI ≥ 27.0 kg/m<sup>2</sup>). The ethics committee at the First Affiliated Hospital of Shanxi Medical University approved the protocol.

### gGFR

On the examination day, patients were well hydrated by water (10 mL/kg), and lay on the table of Infinia scanner (GE Healthcare) after voiding bladder. After a bolus injection of <sup>99m</sup>Tc-DTPA, the renal dynamic protocol (2 s/frame for 1 minute and 15 s/frame for 12 minutes) was immediately initialized. Energy peak was 140 keV, and energy window ± 10%. Following the integral method, ROIs were drawn for kidneys and subrenal background. The counts acquired during 2 to 3 minutes were corrected by background counts and kidney depth (Tonnesen formula). gGFR is calculated by (Equation 1).

$$gGFR = 9.8127 \times (\text{left} + \text{right uptake percentage}) - 6.82519 \quad (1)$$

### pGFR

At 2 hours (T<sub>1</sub>) and 4 hours (T<sub>2</sub>) after the injection, blood samples were withdrawn, and serum was harvested. Using Equation 2, recorded pGFR were calculated.<sup>11–14</sup> Because of

the neglected second exponential, recorded pGFR was corrected by the Brochner–Mortensen formula (Equation 3).<sup>15</sup>

$$pGFRr = \frac{[DT \ln(P_1/P_2)]}{T_1 - T_2} \exp \frac{(T_1 \ln P_2) - (T_2 \ln P_1)}{T_2 - P_1} \quad (2)$$

where D is the injection count of the tracer, T<sub>1</sub> and T<sub>2</sub> the times from the injection to the 1st and the 2nd sampling, respectively, and P<sub>1</sub> and P<sub>2</sub> are the sample counts on T<sub>1</sub> and T<sub>2</sub>, respectively.

$$pGFR = 0.9908 \times pGFRr - 0.001218 \times pGFRr^2 \quad (3)$$

### Statistical Analysis

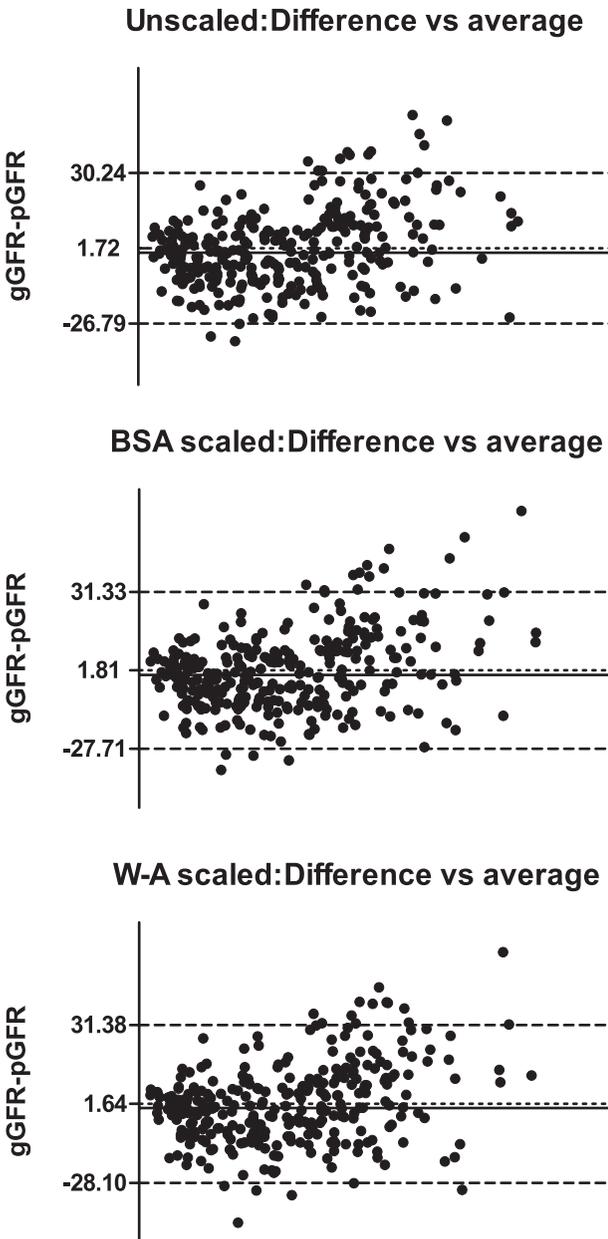
The repeatedly measured GFRs, gGFR, and pGFR were separately scaled to W-A (3.42, mean W-A of enrolled patients) and BSA (1.73 m<sup>2</sup>). Bland–Altman plots were utilized to analyze the agreement between scaled gGFR and scaled pGFR. Systematic differences were determined by the Passing&Bablok regression for no special assumptions regarding the distribution of the samples and the measurement errors.

Normalization ability of index variable was evaluated in 3 patient populations.

- (1) All enrolled patients.
- (2) Because a higher systematic difference might cover the changes of random variation,<sup>5</sup> the 2nd population was the patients with a difference of gGFR and pGFR lower than 30 mL/min.
- (3) Because the accuracy of gGFR decreases in patients with serious renal damage,<sup>16</sup> the 3rd population was the 2nd population after excluding pGFR stage 4 patients.

Considering the similar results of the 3 populations, the results of 2nd and 3rd populations were only presented in the Supplemental Content part, <http://links.lww.com/MD/A616>.

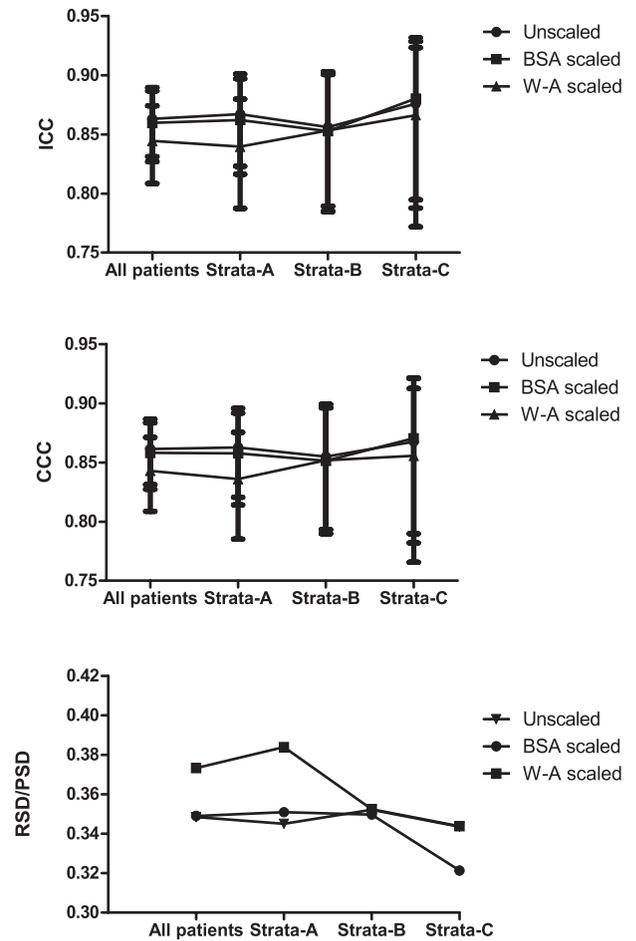
Normalization ability of BSA and W-A was evaluated by intraclass correlation coefficient (ICC), concordance correlation coefficient (CCC), and ratio of residual standard deviation to pooled standard deviation (RSD/PSD). Both ICC and CCC correlate with and are dependent upon between-subject variability (random variation). Because the more between-subjects variability decreased, and the more scaled indices decreased,<sup>17,18</sup> the lower value of ICC (or CCC) indicates the best variable in scaling gGFRs or pGFRs.<sup>5,8</sup> Additionally, RSD/PSD is the ratio of variability that cannot be explained by



**FIGURE 1.** Bland–Altman plots for paired GFRs (mL/min). From the top to the bottom, the plots are for unscaled, BSA and W-A scaled GFRs, respectively. The x-axis and y-axis represent the mean and difference between paired GFRs, respectively. The full line is the mean difference, and the area between the broken lines is the 95% confidence interval. BSA = body surface area, GFR = glomerular filtration rate, W-A = weight-age.

GFR normalization, and the higher ratio indicates the lower between-subjects variability and better normalization ability.

The influence of W-A normalization on GFR values was evaluated by the differences between any 2 of unscaled, BSA scaled, and W-A scaled gGFR (or pGFR). Bias was assessed as the median difference between GFRs, and precision was as the interquartile range of the difference. The bootstrap method was used to calculate 95% confidence intervals for bias. The root-mean square error was also calculated.<sup>19</sup>



**FIGURE 2.** Evaluation of normalization ability. The indices for BMI strata are plotted as estimated values with 95% CI. BMI = body mass index, CI = confidence interval.

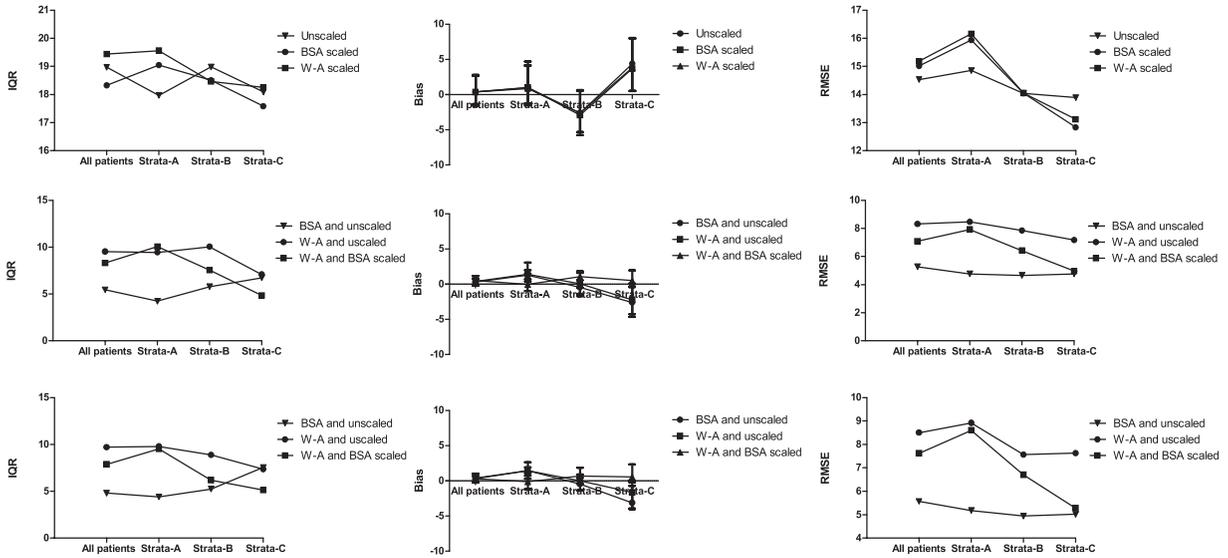
Data were analyzed by SPSS statistical software (IBM, Chicago, IL, version 10.01) and MedCalc package (Mariakerke, Belgium, trial version, v 12.0). A 2-sided  $P < 0.05$  was considered as the significant level.

**RESULTS**

During 2010 to 2014, 298 patients (164 males and 134 females) were recruited and accepted <sup>99m</sup>Tc-DTPA gGFR and pGFR examination. Correlation coefficients of BMI against W-A and BSA were 0.282 and 0.611, respectively. There were 161 and 90 patients in the stratum A and B, respectively. In the stratum C, 32 and 15 patients had a  $27.0 < \text{BMI} < 29.9 \text{ kg/m}^2$  and  $\text{BMI} \geq 30.0 \text{ kg/m}^2$ , respectively. Patient characteristics of the 1st population are listed in Table 1. Among the BMI strata, body weight, BSA, BMI, and W-A had significantly difference, but other variables including both gGFR and pGFR did not (Table 1).

**Evaluation of Normalization Ability**

In the 1st population, there was significant difference between unscaled gGFR and unscaled pGFR ( $t = 2.043$ ,  $P = 0.042$ ). BSA normalization could not eliminate the significance ( $t = 2.073$ ,  $P = 0.039$ ), but W-A normalization could



**FIGURE 3.** Influence of normalization on GFR values. From the first to the third row, plots are for the difference of paired GFRs, the difference of pGFR before and after normalization, and the difference of gGFR before and after normalization, respectively. Median bias is plotted as estimated value with 95% CI, and IQR and RMSE are plotted as the calculated value only. CI=confidence interval, GFR=glomerular filtration rate, gGFR=camera-based glomerular filtration rate, IQR=interquartile range, pGFR=plasma clearance glomerular filtration rate, RMSE=root-mean square error.

( $t = 1.865$ ,  $P = 0.063$ ). The Bland–Altman plots (Figure 1) indicated that both W-A and BSA normalization could slightly enlarge the 95% limits of agreement. On Figure 1, the mean difference between W-A scaled gGFR and pGFR is even smaller than that of unscaled or BSA scaled (see Supplemental Figures 1 and 3, <http://links.lww.com/MD/A616>, Supplemental Content, <http://links.lww.com/MD/A616>, which illustrates the similar results of the 2nd and 3rd populations).

In the 1st population, the indices for evaluating normalization ability are plotted on Figure 2. In each stratum, the normalization ability of W-A was better than that of BSA. However, stratum B was different from other strata in that both BSA and W-A normalization was not obviously better than no normalization. The Passing&Bablok regression indicated that the systematic differences between gGFR and pGFR of stratum B was higher ( $-13.82$  mL/min) than that of the stratum A or C ( $-3.73$  and  $-0.85$  mL/min, respectively). The same results were also found in other populations (see Supplemental Figures 2 and 4, <http://links.lww.com/MD/A616>, Supplemental Content, <http://links.lww.com/MD/A616>, which illustrates the same results in the 2nd and 3rd populations). Therefore, the increased systematic difference of the stratum B covered the obvious changes of random variation eliminated by normalization.<sup>5</sup>

Above all, compared to BSA normalization, W-A performed obviously better than BSA in scaling GFR of renal patients.

### Influence of Normalization on GFR Values

Compared to BSA scaled pGFR stages, 46 patients (15.4%) encountered stage migrations under W-A scaled stages. Of these patients, 23 patients (7.7%) were up-staged, and others (7.7%) were down-staged. No patient was migrated more than 2 stages by either of the normalization method. Additionally, W-A normalization also could not obviously modify BSA scaled gGFR stage.

The differences between any 2 of the unscaled, BSA scaled, and W-A scaled gGFR (or pGFR) were not obviously

changed (Figure 3). In general, interquartile range, bias, and root-mean square error of W-A scaled pGFR (or gGFR) were slightly larger than that of BSA scaled and unscaled pGFR (or gGFR) consequently. However, the median bias between BSA scaled GFRs could even decrease by W-A normalization from 1.00 to 0.86 mL/min in the stratum A, and from 4.37 to 3.81 mL/min in the stratum C.

Above all, W-A normalization could only slightly modify gGFR and pGFR values, and only migrate the BSA stage of a small amount patients.

### DISCUSSION

Our study indicated that W-A was better than BSA in scaling GFR of renal patients without obvious modifying GFR values, and could be applied in clinical application.

BSA normalization is debated in recent years. In clinical practice, it is still valuable to use a powerful index variable. First, GFR normalization can facilitate the comparison among patients, especial those with extreme body size.<sup>20</sup> Second, comparing an individual's GFR to the normal reference range of the general population can be conceived as assessing the extent of renal damage.<sup>1</sup> However, available index variable does not linearly correlate well to GFR of healthy individual.

Using statistical method, a previous study regressed a robust index variable of W-A, which linearly correlated to pGFR of healthy individuals.<sup>7</sup> At a different medical center, the present study confirmed the normalization ability of W-A in renal patients. As a substitute for BSA, scaling GFR to W-A could not significantly modify GFR values, and did not obviously change BSA stages of subjects. In these patients, the normalization could even eliminate the significant difference existed between unscaled gGFR and unscaled pGFR and was better than BSA in decreasing the median bias between scaled GFRs. Therefore, it is possible to apply W-A normalization in routine practice.

Obesity is associated with increased risk of developing chronic kidney diseases, which resulted from the elevated renal plasma flow, renin–angiotensin–aldosterone system activity, and intraglomerular pressure.<sup>21</sup> In the study from Janmahasatian et al,<sup>22</sup> because lean body mass scaled GFR did not exist significant difference between normal weight and obesity, lean body mass performed better than BSA in scaling GFR of obesity. Our data also indicated that W-A normalization performed well in obese patients. In the 3 populations, W-A scaled GFRs had no significant difference between normal weight and obese individual (stratum A and C), and the indices for evaluating normalization ability were obviously improved both in the 2 strata.

Another finding of the present study was that, indicating by the Passing&Bablok regression, the systematic difference between gGFR and pGFR increased only in overweight patients (stratum B). An explanation is that, because of the limited cases of stratum C (n = 47), the increased systematic difference also existed in the stratum. However, in our opinion, after excluding possible sources of systematic difference (the 2nd and 3rd populations), the difference still existed in the stratum B. Therefore, we have reasons to believe that the increased systematic difference resulted from one of the two GFR measurement techniques. Theoretically, because the accuracy and precision of plasma clearance cannot be influenced by body weight of individuals, the increased difference is most likely from the camera-based method. No matter what the reason is, GFR measurement of overweight and obese patients needed to be investigated in future.

Above all, the index variable of W-A, which regressed from healthy individuals, was better than BSA in scaling GFR of renal patients without obvious modifying GFR values.

## CONCLUSION

W-A is better than BSA in scaling GFR without obviously modifying GFR values, and can be applied in routine clinical practice.

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