Comparison of estimated glomerular filtration rate equations at the time of hemodialysis initiation

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ABSTRACT

Background: Estimated glomerular filtration rate (eGFR) is one of the most important guidelines in deciding the optimal timing of dialysis initiation. In the present study, we calculated the eGFR at the time of hemodialysis (HD) initiation using 5 commonly used equations to relate them with clinical and laboratory characteristics of the patients and to evaluate which of these equations best define the eGFR at HD initiation.

Methods: We retrospectively analyzed 409 end-stage renal disease patients who were newly started on HD treatment in our institution. The eGFR was calculated using the Cockcroft-Gault equation, the Cockcroft-Gault equation corrected for body surface area, the Modification of Diet in Renal Disease (MDRD) equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the Nankivell equation.

Results: The mean eGFRs at HD start were significantly different across the equations. The mean eGFR was 7.8 mL/min for the corrected Cockcroft-Gault equation, 7.7 mL/min for the Cockcroft-Gault equation, 6.2 mL/min/1.73 m² for the MDRD equation, and 5.6 mL/min/1.73 m² for the CKD-EPI equation. The corrected Cockcroft-Gault, the MDRD, and the CKD-EPI equations were well correlated with all CKD-specific complications including hypertension, anemia, hyperkalemia, metabolic acidosis, hypocalcemia, hyperphosphatemia, and hyperparathyroidism. The mean eGFR calculated by the corrected Cockcroft-Gault equation showed the lowest coefficient of variation among all the equations.

Conclusions: The eGFR at HD initiation are significantly different according to the used eGFR equations, and the corrected Cockcroft-Gault equation may be the best in defining the eGFR at HD initiation.

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Quality Initiative [2], European [3], Australian [4], and Canadian guidelines [5], recommend the initiation of dialysis when the eGFR is less than 10–15 mL/min. However, recent studies showed that the early dialysis initiation as recommended by these guidelines was not associated with an improvement in clinical outcomes, as compared to the late-start dialysis [6–9].

The Initiating Dialysis Early and Late (IDEAL) study is a prospective, multicenter, randomized, controlled trial to compare outcomes in patients starting dialysis with a higher versus lower eGFR, where the mean eGFR was 12.0 mL/min for the patients who started dialysis early and 9.8 mL/min for those who started dialysis late with the use of the corrected Cockcroft–Gault equation and 9.0 mL/min and 7.2 mL/min, respectively, with the use of the Modification of Diet in Renal Disease (MDRD) equation [6]. Interestingly, the differences between the early-start and the late-start groups (2.2 and 1.8 mL/min) were smaller than the differences created by the 2 equations within the group (3.0 and 2.6 mL/min), which indicates that the discrepancy of the mean eGFR between the 2 equations is too big for the equations to be used interchangeably.

In the present study, we calculated the eGFR at the time of hemodialysis (HD) initiation using 5 commonly used equations including the Cockcroft–Gault equation, the Cockcroft–Gault equation corrected for body surface area, the MDRD equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the Nankivell equation to relate them with clinical and laboratory characteristics of the patients and to evaluate which of these equations best define the eGFR at HD initiation.

Methods

Patients

We retrospectively analyzed ESRD patients who were newly started on HD between January 2010 and December 2012 in our institution. Patients were included if they were 18 years or older and started HD for the first time. Data regarding clinical and demographic characteristics including age, gender, height, weight, systolic and diastolic blood pressures, causes of ESRD, and comorbidities including diabetes mellitus (DM), hypertension, cardiovascular disease (CVD), and congestive heart failure (CHF) were collected from the medical records. DM was defined based on the presence of documented or self-reported history of diabetes or diabetic retinopathy or the presence of diabetic medications in patients’ prescription records. Hypertension was defined in the same way as in DM. This study was approved by the Institutional Review Board of our institution.

Laboratory data

Blood urea nitrogen, creatinine (Cr), bone mineral markers (intact parathyroid hormone, phosphorus, and total calcium), a nutritional marker (albumin), metabolic acidosis markers (bicarbonate), and anemia markers (hemoglobin) were recorded. All laboratory data except intact parathyroid hormone levels were obtained within 1 day before the start of HD. Intact parathyroid hormone levels were obtained within 3 months before the start of HD or within 3 days after the start of HD.

Estimated glomerular filtration rate

For eGFR, we used 5 equations as follows: Cockcroft–Gault equation [10], \(140 - \text{age (years)} \times \left[\text{weight (kg)} \times (0.85 \text{ if female}) / [72 \times \text{serum Cr (mg/dL)}]\right]\); Cockcroft–Gault equation corrected for body surface area, \(140 - \text{age (years)} \times \left[\text{weight (kg)} \times (0.85 \text{ if female}) / [72 \times \text{serum Cr (mg/dL)}] \times 1.73 \text{body surface area (m}^2)\right]\); MDRD equation [11], \(186.3 \times [\text{serum Cr (mg/dL)}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times (0.742 \text{ if female})\); CKD-EPI equation [12], \(141 \times \min \{[\text{serum Cr (mg/dL)}]^{1.2} \times [\text{serum Cr (mg/dL)}] / 0.874, 1\}^{\#} \times \max \{[\text{serum Cr (mg/dL)}]^{1.269} \times 0.993^{\#} \times \text{height (m)} / 1.73, 1\}^{\#} \times 1.018 \times (\text{if female}) \times 0.865 \times 1.159 \times 0.9\}^{\#}\), where \(k\) is 0.7 for females and 0.9 for males, \(a = -0.329\) for females and \(-0.411\) for males, \(\min\) indicates the minimum of Scr/k or 1, and \(\max\) indicates the maximum of Scr/k or 1; Nankivell equation [13], \([6.7/\text{serum Cr (mg/dL)}] + [\text{weight (kg)} / 4 - 100/\text{height (m)}] + (35 \text{ if males and 25 if females})\).

Statistical analysis

Continuous variables are described as means with standard deviation and categorical variables as proportions. Differences between the subgroups were assessed using chi-square tests for categorical variables and Student’s t tests for continuous variables. The coefficient of variation (CV) was calculated as the percent ratio of the standard deviation to the mean. Correlations between variables were assessed by Pearson’s correlation tests. Values of \(P < 0.05\) were considered statistically significant. The analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows 18.0, SPSS Inc., Chicago, IL, USA).

Results

Between January 2010 and December 2012, 1,369 patients who were new to our HD unit were reviewed, and of these, 660 patients were excluded because they had started HD previously in other centers. Other excluded patients were 249 who received HD for acute kidney injury, 17 who received pre-emptive HD for kidney transplantation, 11 who returned to HD after renal allograft failure, and 23 who switched to HD from peritoneal dialysis. Finally, 409 patients who started maintenance HD for ESRD were included in the present analysis. Table 1 summarized the patients’ demographics and the causes of ESRD. The mean age was 58 years, and 52.6% of the patients were men. Comorbidities were common, particularly hypertension (81.9%) and DM (52.8%). The most common causes of ESRD were diabetic nephropathy (48.7%), followed by biopsy-proven glomerulonephritis (11.7%). The mean eGFR at the start of HD was significantly different across the different equations (Table 2). The highest mean eGFR was derived from the corrected Cockcroft–Gault equation \((7.8 \pm 3.6 \text{ mL/min/1.73 m}^2)\) followed by the Cockcroft–Gault \((7.7 \pm 3.8 \text{ mL/min})\), MDRD \((6.2 \pm 3.4 \text{ mL/min/1.73 m}^2)\), CKD-EPI \((5.6 \pm 3.2 \text{ mL/min/1.73 m}^2)\), and finally the Nankivell equation \((0.10 \pm 12.74 \text{ mL/min/1.73 m}^2)\). CV of each eGFR was used to evaluate the extent of variability in relation to the mean eGFR. The results showed that the CV of the corrected Cockcroft–Gault equation (46.0%) was the smallest among the included equations, whereas the Nankivell equation showed the biggest CV (127.4%) despite its lowest eGFR value (Table 2).
Table 1. Baseline characteristics of the patients (N = 409)

| Characteristics                  | Mean ± SD |
|----------------------------------|-----------|
| Age (y)                          | 58.6 ± 14.6 |
| Male gender, n (%)               | 215 (52.6) |
| Weight (kg)                      | 63.2 ± 12.7 |
| BMI (kg/m²)                      | 24.3 ± 9.1 |
| Systolic BP (mmHg)               | 153.2 ± 25.4 |
| Diastolic BP (mmHg)              | 81.6 ± 16.2 |
| Hypertension, n (%)              | 335 (81.9) |
| CVD/CHF, n (%)                   | 79 (19.3) |
| Causes of renal failure, n (%)   |           |
| Diabetic nephropathy             | 197 (48.2) |
| Chronic glomerulonephritis       | 48 (11.7)  |
| Polycystic kidney disease        | 13 (3.2)   |
| Unknown                          | 130 (31.7) |
| Miscellaneous                    | 21 (5.1)   |
| Hemoglobin (g/dL)                | 8.5 ± 1.7  |
| BUN (mg/dL)                      | 97.4 ± 67.7 |
| Creatinine (mg/dL)               | 10.3 ± 5.1 |
| Sodium (mmol/L)                  | 136.7 ± 5.5 |
| Potassium (mmol/L)               | 5.1 ± 1.1  |
| Bicarbonate (mmol/L)             | 15.8 ± 4.6 |
| Calcium (mg/dL)                  | 7.5 ± 1.3  |
| Phosphorus (mg/dL)               | 6.4 ± 2.2  |
| Albumin (g/dL)                   | 3.5 ± 0.6  |
| iPTH (pg/mL)                     | 237.9 ± 173.6 |

Table 2. Comparisons of mean eGFR derived from different equations

|        | Mean ± SD | CV, % | Range     | P       |
|--------|-----------|-------|-----------|---------|
|        |           |       |           | Corrected C-G | MDRD | CKD-EPI | Nankivell |
| C-G    | 7.7 ± 3.8 | 49.5  | 1.9–29.1  | 0.002   | <0.001 | <0.001 | <0.001    |
| Corrected C-G | 7.8 ± 3.6 | 46.0  | 1.9–30.6  | <0.001  | <0.001 | <0.001 | <0.001    |
| MDRD   | 6.2 ± 3.4 | 54.5  | 1.4–23.4  | <0.001  | <0.001 | <0.001 | <0.001    |
| CKD-EPI| 5.6 ± 3.2 | 56.5  | 1.1–23.9  | <0.001  |         |         | <0.001    |
| Nankivell | 0.10 ± 12.74 | 127.4 | -54.1–33.0 |         |         |         |           |

Table 3. Relationships between eGFR- and CKD-specific complications

|        | SBP        | DBP        | Hb         | K          | HCO₃       | Ca         | P          | iPTH       |
|--------|------------|------------|------------|------------|------------|------------|------------|------------|
| C-G    | -0.073     | -0.070     | 0.161**    | -0.161**   | 0.300**    | 0.135**    | -0.399**   | -0.203**   |
| Corrected C-G | -0.115*    | -0.110*    | 0.179**    | -0.182**   | 0.343**    | 0.187**    | -0.461**   | -0.221**   |
| MDRD   | -0.133**   | -0.201**   | 0.204**    | -0.203**   | 0.375**    | 0.242**    | -0.549**   | -0.272**   |
| CKD-EPI| -0.133**   | -0.178**   | 0.198**    | -0.206**   | 0.375**    | 0.232**    | -0.532**   | -0.259**   |
| Nankivell | 0.091      | 0.039      | 0.161**    | -0.095     | 0.241**    | -0.014     | -0.368**   | -0.188**   |

Pearson’s correlation coefficient, *p < 0.05, **p < 0.01.
Ca, serum total calcium; C-G, Cockcroft–Gault; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HCO₃, bicarbonate; iPTH, intact parathyroid hormone; K, potassium; MDRD, Modification of Diet in Renal Disease; P, inorganic phosphate; SBP, systolic blood pressure.
Discussion

In the IDEAL study, dialysis was planned at an eGFR of 5–7 mL/min in the late-start group; however, three-fourths of the patients could not delay the dialysis until this level because of various symptoms including uremia (72.7%), fluid overload (8.7%), malnutrition (1.6%), and hyperkalemia (1.2%), which results in dialysis initiation at a higher eGFR of 9.8 mL/min by the corrected Cockcroft–Gault equation and 7.2 mL/min by the MDRD equation [6]. Because most of our patients started HD based on uremic symptoms and fluid and electrolyte disturbances, it is reasonable to compare them with this late-start group in the IDEAL study. We found that our patients started dialysis at an eGFR of 7.8 mL/min by the corrected Cockcroft–Gault equation and 6.2 mL/min by the MDRD equation, which are lower than the corresponding eGFR in the IDEAL study by 2 mL/min. To exclude cases of early planned HD initiation completely, we separately evaluated the patients who started HD urgently in the ER. The eGFR of these patients were 7.7 mL/min by the corrected Cockcroft–Gault equation and 6.3 mL/min by the MDRD equation, which was similar to the eGFRs of the total patients. The difference of eGFR between our patients and the IDEAL patients may indicate that either our patients develop symptoms at a lower eGFR or report symptoms later, as compared with patients in the West.

Fluid overload accounted for 38.4% of HD initiation, as compared with 8.7% in the IDEAL study. This suggests that sodium intake of our patients may be higher than that of Western patients because of a higher content of sodium in Korean food.

In addition, we evaluated the eGFR according to different clinical situations: patients with DM versus without DM and outpatient clinic patients versus ER patients. DM patients started HD at a significantly higher eGFR than non-DM patients, which may be due to the higher proportion of fluid overload in DM (44.9%) than that in non-DM patients (31.4%). In our experience, it is more difficult to tolerate fluid overload than uremic symptoms. It is possible that the higher eGFR in DM patients should contribute to the less-severe metabolic acidosis, hyperphosphatemia, and hyperparathyroidism in these patients. Accordingly, the United States Renal Data System (USRDS) data showed that the early initiation of dialysis is associated with the presence of DM [14].

The patients who present to the ER are usually in more urgent need of HD than clinic patients. Therefore, it is conceivable that ER patients may have lower eGFR than the clinic patients. However, we found that both groups were comparable in eGFR. ER patients were older and had more disturbances of fluid balance, serum potassium, and serum bicarbonate levels, as compared to clinic patients, which might explain the more urgent need for dialysis in ER patients. The higher incidence of CVDs/CHF in DM and ER groups should have contributed to the higher proportion of volume overload as a reason for dialysis start in these groups.
Regarding the equation that best defines the eGFR value at HD initiation, our finding suggests that the corrected Cockcroft–Gault equation, which was adopted in the IDEAL study, may best fit the purpose because of its good correlations with CKD-specific complications and the smallest dispersion (coefficient variation). In addition, our data indicate that the Nankivell equations that were originally developed for kidney transplants should not be used in CKD patients given its high dispersion and irrelevance to CKD-specific complications. The poor performance of the Nankivell equation may be explained by its development from the transplant population and the inclusion of blood urea nitrogen as one of the variables unlike the other equations [13].

A limitation of this study is that we were not successful in defining the best eGFR in the subgroups such as DM or ER groups because the reduced sample sizes of the subgroups were not big enough to make the statistical analysis adequately powered. Another limitation is that we do not have data on GFR using 24-hour urine Cr clearance or radioisotope renal scans to compare with each eGFR. A larger prospective study with the actual measurement of GFR is required to better evaluate the utility of various eGFRs at the time of HD initiation.

In summary, we showed that the mean eGFR at HD start was significantly different across the equations. The mean eGFR ranged between 5.6 and 7.8 mL/min according to the 4 eGFR equations, excluding the Nankivell equation. The Nankivell equation was not suitable for CKD patients. The corrected Cockcroft–Gault, the MDRD, and the CKD-EPI equations were well correlated with all CKD-specific complications. The mean eGFR by the corrected Cockcroft–Gault equation showed the lowest dispersion among all equations. DM patients started HD at a higher eGFR than non-DM patients, and the patients who underwent emergent HD in ER did not differ in eGFR, as compared with the nonemergent patients. This study was not designed to evaluate the optimal timing of dialysis initiation; hence, the eGFR in this study is not an indication for the initiation of dialysis.

This study is potentially a valuable reference in the management of CKD patients and in the design of the future studies for the optimal timing of dialysis initiation.

Conflicts of interest

All authors have no conflicts of interest to declare.

Author contributions

Dr. Shin had full access to the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and statistical analysis were done by Drs. Shin and Lee; critical revision of the manuscript for important intellectual content was carried out by all authors and administrative, technical, and material support was also provided by everyone. Study supervision was done by Drs. Shin and Kim (KHS). All authors have contributed to the paper.

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